A METHOD FOR THE PROPHYLAXIS AND/OR TREATMENT OF MEDICAL DISORDERS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U. S. Application Ser. No. 60/140,345, the disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates generally to a method for the prophylaxis and/or treatment of medical disorders, and in particular proliferative and/or inflammatory skin disorders, and to genetic molecules useful for same. The present invention is particularly directed to genetic molecules capable of modulating growth factor interaction with its receptor on cells such as epidermal keratinocytes to inhibit, reduce or otherwise decrease stimulation of this layer of cells. The present invention contemplates, in a particularly preferred embodiment, a method for the prophylaxis and/or treatment of psoriasis or neovascularization conditions such as neovascularization of the retina. The present invention is further directed to the subject genetic molecules in adjunctive therapy for epidermal hyperplasia, such as in combination with UV treatment, and to facilitate apoptosis of cancer cells and in particular cancer cells comprising keratinocytes.

BACKGROUND OF THE INVENTION

Bibliographic details of the publications numerically referred to in this specification are collected at the end of the description.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia or any other country.

Psoriasis and other similar conditions are common and often distressing proliferative and/or inflammatory skin disorders affecting or having the potential to affect a significant proportion

of the population. The condition arises from over proliferation of basal keratinocytes in the epidermal layer of the skin associated with inflammation in the underlying dermis. Whilst a range of treatments have been developed, none is completely effective and free of adverse side effects. Although the underlying cause of psoriasis remains elusive, there is some consensus of opinion that the condition arises at least in part from over expression of local growth factors and their interaction with their receptors supporting keratinocyte proliferation *via* keratinocyte receptors which appear to be more abundant during psoriasis.

One important group of growth factors are the dermally-derived insulin-like growth factors (IGFs) which support keratinocyte proliferation. In particular, IGF-I and IGF-II are ubiquitous peptides each with potent mitogenic effects on a broad range of cells. Molecules of the IGF type are also known as "progression factors" promoting "competent" cells through DNA synthesis. The IGFs act through a common receptor known as the Type I or IGF-I receptor, which is tyrosine kinase linked. They are synthesised in mesenchymal tissues, including the dermis, and act on adjacent cells of mesodermal, endodermal or ectodermal origin. The regulation of their synthesis involves growth hormone (GH) in the liver, but is poorly defined in most tissues [1].

Particular proteins, referred to as IGF binding proteins (IGFBPs), appear to be involved in autocrine/paracrine regulation of tissue IGF availability [2]. Six IGFBPs have so far been identified. The exact effects of the IGFBPs is not clear and observed effects *in vitro* have been inhibitory or stimulatory depending on the experimental method employed [3]. There is some evidence, however, that certain IGFBPs are involved in targeting IGF-I to its cell surface receptor.

Skin, comprising epidermis and underlying dermis, has GH receptors on dermal fibroblasts [4]. Fibroblasts synthesize IGF-I as well as IGFBPs-3, -4, -5 and -6 [5] which may be involved in targeting IGF-I to adjacent cells as well as to the overlaying epidermis. The major epidermal

cell type, the keratinocyte, does not synthesize IGF-I, but possesses IGF-I receptors and is responsive to IGF-I [6].

It is apparent, therefore, that IGF-I and other growth promoting molecules, are responsible for or at least participate in a range of skin cell activities. In accordance with the present invention, the inventors have established that aberrations in the normal functioning of these molecules or aberrations in their interaction with their receptors is an important factor in a variety of medical disorders such as proliferative and/or inflammatory skin disorders. It is proposed, therefore, to target these molecules or other molecules which facilitate their functioning or interaction with their receptors to thereby ameliorate the effects of aberrant activity during or leading to skin disease conditions and other medical conditions such as those involving neovascularization. Furthermore, these molecules may also be used to facilitate apoptosis of target cells and may be useful as adjunctive therapy for epidermal hyperplasia.

SUMMARY OF THE INVENTION

Nucleotide and amino acid sequences are referred to by a sequence identifier, i.e. ~~(<400>1),~~ (SEQ ID NO:1) ~~(<400>2),~~ (SEQ ID NO:2) etc. A sequence listing is provided after the claims.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

Accordingly, one aspect of the present invention contemplates a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation or a cell otherwise involved in the said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof

capable of inhibiting or otherwise reducing a growth factor mediated cell proliferation and/or inflammation and/or other medical disorder.

According to this preferred embodiment, there is provided a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation or a cell otherwise involved with said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation and/or other medical disorder.

According to this embodiment, there is provided a method for ameliorating the effects of a proliferative and/or inflammatory skin disorder such as psoriasis said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation with effective amounts of UV treatment and a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation.

According to this embodiment, there is provided in a particularly preferred aspect a ribozyme comprising a hybridising region and a catalytic region wherein the hybridising region is capable of hybridising to at least part of a target mRNA sequence transcribed from a genomic gene corresponding to ~~<400>1 or <400>2~~ SEQ ID NO. 1 or SEQ ID NO. 2 wherein said catalytic domain is capable of cleaving said target mRNA sequence to reduce or inhibit IGF-I mediated cell proliferation and/or inflammation and/or other medical disorders.

Yet another aspect of the present invention contemplates co-suppression to reduce expression or to inhibit translation of an endogenous gene encoding, for example, IGF-I, its receptor, or IGFBPs such as IGFBP-2 and/or -3. In co-suppression, a second copy of an endogenous gene or a substantially similar copy or analogue of an endogenous gene is introduced into a cell

following topical administration. As with antisense molecules, nucleic acid molecules defining a ribozyme or nucleic acid molecules useful in co-suppression may first be protected such as by using a nonionic backbone.

Another aspect of the present invention contemplates a pharmaceutical composition for topical administration which comprises a nucleic acid molecule capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation such as psoriasis and one or more pharmaceutically acceptable carriers and/or diluents.

Yet another aspect of the present invention contemplates the use of a nucleic acid molecule in the manufacture of a medicament for the treatment of proliferative and/or inflammatory skin disorders or other medical disorders mediated by a growth factor.

Still a further aspect of the present invention contemplates an agent comprising a nucleic acid molecule as hereinbefore defined useful in the treatment of proliferative and/or inflammatory skin disorders, such as psoriasis or other medical disorder..

The present invention further contemplates the use of the genetic molecules and in particular the antisense molecules to inhibit the anti-apoptotic activity of IGF-I receptor.

BRIEF DESCRIPTION OF THE FIGURES

(SEQ ID NO. 1)

Figure 1 is a representation of the nucleotide sequence of IGFBP-2.

```
LOCUS       HSIGFBP2     1433 bp    RNA              PRI       31-JAN-1990
DEFINITION  Human mRNA for insulin-like growth factor binding protein (IGFBP-2)
ACCESSION   X16302
KEYWORDS    insulin-like growth factor binding protein.
SOURCE      human
  ORGANISM  Homo sapiens
            Eukaryota; Animalia; Metazoa; Chordata; Vertebrata; Mammalia;
            Theria; Eutheria; Primates; Haplorhini; Catarrhini; Hominidae.
REFERENCE   1  (bases 1 to 1433)
  AUTHORS   Binkert,C., Landwehr,J., Mary,J.L., Schwander,J. and Heinrich,G.
  TITLE     Cloning, sequence analysis and expression of a cDNA encoding a
            novel insulin-like growth factor binding protein (IGFBP-2)
  JOURNAL   EMBO J. 8, 2497-2502 (1989)
  STANDARD  full automatic
COMMENT     NCBI gi: 33009
FEATURES             Location/Qualifiers
     source          1. .1433
                     /organism="Homo sapiens"
                     /dev_stage="fetal"
                     /tissue_type="liver"
     misc_feature    1416. .1420
                     /note="pot. polyadenylation signal"
     polyA_site      1433
                     /note="polyadenylation site"
     CDS             118. .1104
                     /note="precursor polypeptide;  (AA -39 to 289);  NCBI gi:
                     33010."
                     /codon_start=1
                     /translation="MLPRVGCPALPLPPPPLLPLLPLLLLLLGASGGGGGARAEVLFR
                     CPPCTPERLAACGPPPVAPPAAVAAVAGGARMPCAELVREPGCGCCSVCARLEGEACG
                     VYTPRCGQGLRCYPHPGSELPLQALVMGEGTCEKRRDAEYGASPEQVADNGDDHSEGG
                     LVENHVDSTMNMLGGGGSAGRKPLKSGMKELAVFREKVTEQHRQMGKGGKHHLGLEEP
                     KKLRPPPARTPCQQELDQVLERISTMRLPDERGPLEHLYSLHIPNCDKHGLYNLKQCK
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                     (<400>21)
     CDS             118. .234
                     /note="signal peptide;  (AA -39 to -1);  NCBI gi: 33011."
                     /codon_start=1
                     /translation="MLPRVGCPALPLPPPPLLPLLPLLLLLLGASGGGGGARA"
                     (<400>22)
     CDS             235. .1101
                     /note="mature IGFBP-2;  (AA 1 to 289);  NCBI gi: 33012."
                     /codon_start=1
                     /translation="EVLFRCPPCTPERLAACGPPPVAPPAAVAAVAGGARMPCAELVR
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                                    EPGCGCCSVCARLEGEACGVYTPRCGQGLRCYPHPGSELPLQALVMGEGTCEKRRDAE
                                    YGASPEQVADNGDDHSEGGLVENHVDSTMNMLGGGGSAGRKPLKSGMKELAVFREKVT
                                    EQHRQMGKGGKHHLGLEEPKKLRPPPARTPCQQELDQVLERISTMRLPDERGPLEHLY
                                    SLHIPNCDKHGLYNLKQCKMSLNGQRGECWCVNPNTGKLIQGAPTIRGDPECHLFYNE
                                    QQEACGVHTQRMQ" (<400>23)
BASE COUNT      239 a    466 c    501 g    227 t
ORIGIN

HSIGFBP2  Length: 1433  May 11, 1994  10:06  Type: N  Check: 6232  ..
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(SEQ ID NO. 2)

Figure 2 is a representation of the nucleotide sequence of IGFBP-3.

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LOCUS       HUMGFIBPA    2474 bp ss-mRNA            PRI       15-JUN-1990
DEFINITION  Human growth hormone-dependent insulin-like growth factor-binding
            protein mRNA, complete cds.
ACCESSION   M31159
KEYWORDS    insulin-like growth factor binding protein.
SOURCE      Human plasma, cDNA to mRNA, clone BP-53.
  ORGANISM  Homo sapiens
            Eukaryota; Animalia; Chordata; Vertebrata; Mammalia; Theria;
            Eutheria; Primates; Haplorhini; Catarrhini; Hominidae.
REFERENCE   1  (bases 1 to 2474)
  AUTHORS   Wood,W.I., Cachianes,G., Henzel,W.J., Winslow,G.A., Spencer,S.A.,
            Hellmiss,R., Martin,J.L. and Baxter,R.C.
  TITLE     Cloning and expression of the growth hormone-dependent insulin-like
            growth factor-binding protein
  JOURNAL   Mol. Endocrinol. 2, 1176-1185 (1988)
  STANDARD  full automatic
COMMENT     NCBI gi: 183115
FEATURES             Location/Qualifiers
     mRNA            <1. .2474
                     /note="GFIBP mRNA"
     CDS             110. .985
                     /gene="IGFBP1"
                     /note="insulin-like growth factor-binding protein;  NCBI
                     gi: 183116."
                     /codon_start=1
                     /translation="MQRARPTLWAAALTLLVLLRGPPVARAGASSGGLGPVVRCEPCD
                     ARALAQCAPPPAVCAELVREPGCGCCLTCALSEGQPCGIYTERCGSGLRCQPSPDEAR
                     PLQALLDGRGLCVNASAVSRLRAYLLPAPPAPGNASESEEDRSAGSVESPSVSSTHRV
                     SDPKFHPLHSKIIIIKKGHAKDSQRYKVDYESQSTDTQNFSSESKRETEYGPCRREME
                     DTLNHLKFLNVLSPRGVHIPNCDKKGFYKKKQCRPSKGRKRGFCWCVDKYGQPLPGYT
                     TKGKEDVHCYSMQSK" (<400>24>)
     source          1. .2474
                     /organism="Homo sapiens"
BASE COUNT      597 a    646 c    651 g    580 t
ORIGIN
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HUMGFIBPA Length: 2494 May 11, 1994 10:00 Type: N Check: 9946 ..

(SEQ ID NO.3)

Figure 3 is a representation of the nucleotide sequence of IGF-1-receptor.

```
LOCUS       HSIGFIRR     4989 bp    RNA              PRI       28-MAR-1991
DEFINITION  Human mRNA for insulin-like growth factor I receptor
ACCESSION   X04434 M24599
KEYWORDS    glycoprotein; insulin receptor;
            insulin-like growth factor I receptor; membrane glycoprotein;
            receptor; tyrosine kinase.
SOURCE      human
  ORGANISM  Homo sapiens
            Eukaryota; Animalia; Metazoa; Chordata; Vertebrata; Mammalia;
            Theria; Eutheria; Primates; Haplorhini; Catarrhini; Hominidae.
REFERENCE   1  (bases 1 to 4989)
  AUTHORS   Ullrich,A., Gray,A., Tam,A.W., Yang-Feng,T., Tsubokawa,M.,
            Collins,C., Henzel,W., Bon,T.L., Kathuria,S., Chen,E., Jakobs,S.,
            Francke,U., Ramachandran,J. and Fujita-Yamaguchi,Y.
  TITLE     Insulin-like growth factor I receptor primary structure: comparison
            with insulin receptor suggests structural dererminants that define
            functional specificity
  JOURNAL   EMBO J. 5, 2503-2512 (1986)
  STANDARD  full automatic
COMMENT     NCBI gi: 33058
FEATURES             Location/Qualifiers
     source          1. .4989
                     /organism="Homo sapiens"
                     /tissue_type="placenta"
                     /clone_lib="(lamda)gt10"
                     /clone="(lambda)IGF-1-R.85, (lambda)IGF-1-R.76"
     sig_peptide     32. .121
     mat_peptide     122. .4132
                     /note="IGF-I receptor"
     misc_feature    122. .2251
                     /note="alpha-subunit (AA 1 - 710)"
     misc_feature    182. .190
                     /note="pot.N-linked glycosylation site (AA 21 - 23)"
     misc_feature    335. .343
                     /note="pot.N-linked glycostlation site (AA 72 - 74)"
     misc_feature    434. .442
                     /note="pot.N-linked glycostlation site (AA 105 - 107)"
     misc_feature    761. .769
                     /note="pot.N-linked glycostlation site (AA 214 - 216)"
     misc_feature    971. .979
                     /note="pot.N-linked glycostlation site (AA 284 - 286)"
     misc_feature    1280. .1288
                     /note="pot.N-linked glycostlation site (AA 387 - 389)"
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misc_feature    1343. .1351
                /note="pot.N-linked glycosylation site (AA 408 - 410)"
misc_feature    1631. .1639
                /note="pot.N-linked glycostlation site (AA 504 - 506)"
misc_feature    1850. .1858
                /note="pot.N-linked glycosylation site (AA 577 - 579)"
misc_feature    1895. .1903
                /note="pot.N-linked glycosylation site (AA 592 - 594)"
misc_feature    1949. .1957
                /note="pot.N-linked glycosylation site (AA 610 - 612)"
misc_feature    2240. .2251
                /note="putative proreceptor processing site (AA 707 -
                710)"
misc_feature    2252. .4132
                /note="beta-subunit (AA 711 - 1337)"
misc_feature    2270. .2278
                /note="pot.N-linked glycosylation site (AA 717 - 719]"
misc_feature    2297. .2305
                /note="pot.N-linked glycosylation site (AA 726 - 728)"
misc_feature    2321. .2329
                /note="pot.N-linked glycosylation site (AA 734 - 736)"
misc_feature    2729. .2737
                /note="pot.N-linked glycosylation site (AA 870 - 872)"
misc_feature    2768. .2776
                /note="pot.N-linked glycosylation site (AA 883 - 885)"
misc_feature    2837. .2908
                /note="transmembrane region (AA 906 - 929)"
misc_feature    2918. .2926
                /note="pot.N-linked glycosylation site (AA 933 - 935)"
misc_feature    3047. .3049
                /note="pot.ATP binding site (AA 976)"
misc_feature    3053. .3055
                /note="pot.ATP binding site (AA 978)"
misc_feature    3062. .3064
                /note="pot.ATP binding site (AA 981)"
misc_feature    3128. .3130
                /note="pot.ATP binding site (AA 1003)"
CDS             32. .4132
                /product="IGF-I receptor"
                /note="50 stops when translation attempted, frame 1, code
                0"
BASE COUNT      1216 a   1371 c   1320 g   1082 t
ORIGIN

HSIGFIRR  Length: 4989  May 11, 1994  12:10  Type: N  Check: 133  ..
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Figure 4A is a photographic representation of a Western ligand blot of HaCaT conditioned medium showing IGFBP-3 secreted in 24 hours after 7 day treatment with phosphorothioate oligonucleotides (BP3AS2, BP3AS3 and BP3S) at 0.5μM and 5μM;

* no oligonucleotide added.

Figure 4B is a graphical representation of a scanning imaging desitometry of Western ligand blot (Figure 4A), showing relative band intensities of IGFBP-3 and the 24kDa IGFBP-4 after treatment with phosphorothioate oligonucleotides;

* no oligonucleotide added.

Figure 5A is a photographic representation of a Western ligand blot of HaCaT conditioned medium showing IGFBP-3 secreted in 24 hours after 7 day treatment with phosophorothioate oligonucleotide BP3AS2 at 0.5μM compared with several control oligonucleotides at 0.5μM. (a) oligonucleotide BP3AS2NS; (b) oligonucleotide BP3AS4; (c) oligonucleotide BP3AS4NS; and (untreated), no oligonucleotide added.

Figure 5B is a graphical representation of a scanning imaging densitometry of Western ligand blot (Figure 5A), showing relative band intensities of IGFBP-3 after treatment with phosphorothioate oligonucleotides as in Figure 5A, showing IGFBP-3 band intensities expressed as a percentage of the average band intensity from conditioned medium of cells not treated with oligonucleotide.

Figure 6 is a graphical representation showing inhibition of IGF-I binding by antisense oligonucleotides to IGF-I receptor. IGFR.AS: antisense; IGFR.S: sense.

Figure 7 is a graphical representation showing inhibition of IGFBP-3 production in culture medium following initial treatment with antisense oligonucleotides once daily over a 2 day period.

Figure 8 is a graphical representation showing optimization of IGFBP-3 antisense oligonucleotide concentration as determined by relative IGFBP-3 concentration in culture medium.

Figure 9 is a diagramatic representation of a map of IGF-1 Receptor mRNA and position of target ODNs.

Figure 10 is a photographical representation showing Lipid-mediated uptake of oligonucleotide in keratinocytes. HaCaT keratinocytes were incubated for 24 hours in medium (DMEM plus 10% v/v FCS) containing fluorescently labelled ODN (R451, 30 nM) and cytofectin GSV (2 μg/ml). The cells were then transferred to ODN-free medium and fluorescence microscopy (a) and phase contrast (b) images of the cells were obtained.

Figure 11 is a graphical representation of uptake (A) and toxicity (B) of ODN/lipid complexes in keratinocytes. Confluence HaCaT keratinocytes were incubated in DMEM containing fluoresently labelled ODN (R451) plus liposome over 120 hours, viewed using fluorescene microscopy and trypan blue stained and counted.

Figure 12 is a graphical representation of an IGF-1 Receptor mRNA in ODN treated (30nM) HaCaT cells (2μg/ml GSV). HaCaT keratinocytes were treated for 96 hours with C-5 propynyl, dU, dC ODNs complexed with cytofectin GSV. Cells were treated with ODNs complementary to the human IGF-I receptor mRNA (27, 32, 74 and 78), 2 randomised sequence ODNs (R451) and R766), liposome alone (GSV) or were left untreated (UT). Total RNA was isolated then analysed for IGF-I receptor mRNA and GAPDH mRNA levels by RNase Protection and Phosphorlmager quantitiation.

(A) Electrophoretic analysis of IGF-I receptor and GAPDH mRNA fragments after RNase Protection. Molecular weight markers are shown on the right hand side. Full length probe

is shown on the left hand side (G-probe and I-probe). GAPDH protected fragments (G) are seen at 316 bases and IGF-I receptor protected fragments (I) are seen at 276 bases.

(B) Relative level of IGF-I receptor mRNA following each treatment is shown.

Figure 13 is a graphical representation of an IGF-1 receptor mRNA in ODN treated (30nM) HaCaT cells (2μg/ml GSV). Summary of IGF-I receptor ODN screening data. HaCaT keratinocytes were treated for 96 hours with C-5 propynyl, dU, dC ODNs complexed with cytofectin GSV. Total RNA was isolated then analysed for IGF-I receptor mRNA and GAPDH mRNA levels by RNase protection and phosphorImager quantitiation. Relative level of IGF-I receptor mRNA is shown after treatment with ODNs complementary to the human IGF-I receptor mRNA, 4 randomised sequence ODNs and liposome alone. (26-86=IGF-I receptor ODNs; R1, R4, R7 and R9 = randomised ODNs (R1=R121, R4=R451, R7=R766, R9=R961); GSV=liposome alone; UT=untreated). *indicates a significant difference in relative IGF-I receptor mRNA from GSV treated cells (n=4-10, $p<0.05$).

Figure 14 is a graphical representation of the effect of antisense oligonucleotides on IGF-1 receptor levels on the surface of keratinocytes. HaCaT cells were grown to confluence in 24-well plates in DMEM containing 10% v/v FCS. Oligodeoxynucleotide (ODN) and Cytofectin GSV (GSV, Glen Research) were mixed together in serum-free DMEM, incubated at room temperature for 10 minutes before being diluted ten-fold in medium and placed on the cells. Cells were incubated for 72 hours with 30 nM random sequence or antisense ODN and 2 μg/ml GSV or with GSV alone in DMEM containing 10% v/v FCS with solutions replaced every 24 hours. This was followed by incubation with ODN/GSV in serum-free DMEM for 48 hours. All incubations were performed at 37°C. Wells were washed twice with 1 ml cold PBS. Serum-free DMEM containing 10^{-10}M ^{125}I-IGF-I was added with or without the IGF-I analogue, des (1-3) IGF-I, at 10^{-10}M to 10^{-7}M. Cells were incubated at 4°C for 17 hours with gentle shaking then washed three times with 1 ml cold PBS and lysed in 250 μl 0.5M

NaOH/0.1% v/v Triton X-100 at room temperature for 4 hours. Specific binding of the solubilised cell extract was measured using a γ counter.

Figure 15 is a graphical representation of the effect of antisense oligonucleotides on IGF-1 receptor levels on the surface of keratinocytes.

Figure 16 is a photographical representation of H & E stained sections of (A) psoriatic skin biopsy prior to grafting and (B) 49 day old psoriatic skin graft using skin from the same donor.

Figure 17 is a photographical representation of uptake of oligonucleotide after intradermal injection into psoriatic skin graft on a nude mouse. Psoriatic skin graft was intradermally injected with ODN (R451, 50 μl, 10 μM). The graft was removed and sectioned after 24 hours, then viewed using confocal microscopy.

Figure 18(a) is a photographical representation of Pregraft, Donor JH, Donor JH, PBS treated, 50μl, Donor JH, #50 treated, 50μl, 10μM.

Figure 18(b) is a photographical representation of Donor LB, pregraft, Donor LB, PBS treated (50μl), Donor LB, #74 treated (50μl, 10μM).

Figure 18(c) is a photographical representation of Donor PW, pregraft, Donor PW, R451 treated (50μl, 10μM), Donor LB, #74 treated (50μl, 10μM).

Figure 18(d) is a photographical representation of Donor GM, pregraft, Donor GB, R451 treated (50μl, 10μM), Donor GM, #27 treated (50μl, 10μM).

Figure 19(a) is a photographical representation showing Donor JH pregraft, Donor JH PBS treated 50μl, Donor JH #50 treated 50μl, 10μM.

Figure 19(b) is a photographical representation Donor LB pregraft, Donor LB PBS treated 50μl, Donor LB #74 treated 50μl, 10μM.

Figure 19(c) is a photographical representational showing Donor PW pregraft, Donor PW r451 treated 50μl, 10μM, Donor PW #74 treated 50μl, 10μM.

Figure 19(d) is a photographical representation showing Donor GM pregraft, Donor GM R451 treated 50μl, 10μM, Donor #27 treated 50μl, 10μM.

Figure 20 is a graphical representation showing suppression of psoriasis after treatment with oligonucleotide (quantification). Oligonucleotide (50 μl, 10μM) was injected every two days for 20 days, as were control treatments. Skin thickness was measured by removing the skin and using computer software (MCID analysis) to measure the exact thickness of each graft. N=3-4 for each treatment. *indicates a significant difference from the pregraft value (ANOVA, $P<0.05$)

Figure 21 is a photographic representation of αhKi-67 imunobiological binding.

Figure 22 is a photographical representation showing penetration of oligonucleotide into human skin after topical treatment. Fluorescently labelled oligonucleotide (10 μM R451) was applied topically after formulation with cytofectin GSV (10 μg/ml) and viewed using confocal microscopy.

Figure 23 is a photographical representation showing penetration of oligonucleotide into human skin after application of topical gel formation. Fluorescently labelled oligonucleotide

(10 μM R451) was applied topically after complexing with cytofectin GSV (10 μg/ml) and formulation into 3% methylcellulose gel. Image was obtained using confocal microscopy.

Figure 24 is a graphical representation showing IGFBP-3 mRNA.

Figure 25(a) is a graphical representation showing IGFBP-3 mRNA in AON treated (100nM) HaCaT cells (2μg/ml GSV).

Figure 25(b) is a graphical representation showing IGFBP-3 mRNA levels of AON treated (100nm) HaCaT cells (2μg/ml GSV).

Figure 25(c) is a graphical representation showing IGFBP-3 mRNA in AON treated (30nM) HaCaT cells (2μg/ml GSV).

Figure 25(d) is a graphical representation showing IGFBP-3 mRNA in AON treated (30nM) HaCaT cells (2μg/ml GSV).

Figure 26(a) is a graphical representation showing IGFBP-3 mRNA in ODN treated (30nM) HaCaT cells (2μg/ml). HaCaT keratinocytes were treated for 51 hours with C-5 propynl, dU, dC ODNs complexed with cytofectin GSV. Total RNA was isolated then analysed for IGFBP-3 mRNA and GAPDH mRNA levels by Northern analysis and phosphorimager quantitation. Relative level of IGFBP-3 mRNA is shown after treatment with ODNs complementary to the human IGFBP-3 mRNA, 4 randomised sequence ODNs and lipsome alone. (1-24=IGFBP-3 ODNs; R1, R4, R7 and R9=randomised ODNs (R1=R121, R4=R451, R7=R766, R9 R961); GS=liposome alone; UT=untreated). *indicates a significant different in relative IGFBP-3 mRNA from GSV treated cells (n- 5-8, $p<0.01$), **indicates a significant difference in relative IGFBP-3 mRNA from GSV treated cells (n= 5-8, $p<0.05$).

Figure 26(b) is a graphical representation showing IGFBP-3 mRNA in ODN treated (100nM) HaCaT cells (2μg/ml GSV). HaCaT keratinocytes were treated for 51 hours with C-5 propynl, dU, dC ODNs complexed with cytofectin GSV. Total RNA was isolated then analysed for IGFBP-3 mRNA and GAPDH mRNA levels by Northern analysis and phosphorimager quantitation. Relative level of IGFBP-3 mRNA is shown after treatment with ODNs complementary to the human IGFBP-3 mRNA, 4 randomised sequence ODNs and liposome alone. (1-24=IGFBP-3 ODNs; R1, R4, R7 and R9 = randomised ODNs (R1-R121, R4=R451, R7=R766, R9-R961), GS=lipsome alone; UT=untreated). *indicates a significant difference in relative IGFBP-3 mRNA from GSV treated cells (n- 6-8, $p<0.01$).

Figure 27 is a representation showing a reduction in IGF-I receptor mRNA in HaCaT cells following treatment with antisense oligonucleotides. Confluent HaCaT cells were treated every 24 h for 4 days with 2 μg/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific oligonucleotides *(#26 to #86)* or random sequence oligonucleotides (R121, R451 and R766). Total RNA was isolated and analysed for IGF-I receptor and GAPDH mRNA by RNase protection assay. (a). Representative RNase protection assay gel showing IGF-I receptor *(IGF*R) and GAPDH mRNA in untreated or treated HaCaT cells. In this example, a reduction in IGFR band intensity relative to GAPDH can be seen with AON #27 and #78, but not with #32, #74 or the controls *(R*4, *R*7, random oligonucleotides R451 and R766, respectively; G, GSV lipid; *U*T, untreated).

(b) Densitometric quantitation of IGF-I receptor mRNA (normalised to GAPDH mRNA) in HaCaT cells following treatment with IGF-I receptor specific oligonucleotides (solid black), random sequence oligonucleotides (horizontal striped bar) or GSV alone (shaded bar) compared to untreated cells *(U*T, vertical striped bar). Each oligonucleotide was assayed in duplicate in at least two separate experiments.

Results are presented as mean ± SEM. A one-way ANOVA followed by Tukey's (▲) test was performed; ▲ indicates a significant difference between cells treated with IGF-I receptor

specific AONs and all of the control treatments ($p<0.05$). n=4 except for #27 and #32 (n=6); #28 and #68 (n=3), R766 (n=9), and R451, GSV and untreated (n=10).

Figure 28 is a representation showing a reduction in total cellular IGF-I receptor protein following antisense oligonucleotide treatment. Confluent HaCaT cells were treated every 24 h for 4 days with 2 μg/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific AONs (#27, #50 and #64) or the random sequence oligonucleotide, R451. Total cellular protein was isolated and analysed for IGF-I receptor by SDS PAGE followed by western blotting with an antibody specific for the human IGF-I receptor. **(a)** Duplicate treated cellular extracts showing the IGF-I receptor at the predicted size of 110 kD

(b) Densitometric quantitation of IGF-I receptor protein. Results are presented as mean ± SEM of four different experiments each performed in duplicate. A one-way ANOVA followed by a Dunnett's test was performed; * indicates a significant difference from GSV treated cells ($p<0.01$). *GSV*, GSV lipid alone; *UT*, untreated; R451, random sequence oligonucleotide; *64*, *50*, *27*, IGF-I receptor-specific AONs.

Figure 29 is a representation showing a reduction in IGF-I receptor numbers on the keratinocyte cell surface after antisense oligonucleotide treatment. HaCaT cells were transfected with IGF-I receptor specific AONs #27 (—▲—), #50 (—x—), #64 (---■---), a random sequence oligonucleotide R451 (—o—), or treated with GSV lipid alone (--□--) every 24 h for four days (untreated cells, --✳--). Competition binding assays using ^{125}I-IGF-I and the receptor-specific analogue, des(1-3)IGF-I, were performed (inset); plotted values are means ± standard error. The mean values were then subjected to Scatchard analysis.

Figure 30 is a representation showing a reduction in keratinocyte cell number following antisense oligonucleotide treatment. HaCaT cells, initially at 40% confluence, were transfected with the IGF-I receptor specific AON #64, control sequences R451 and 6416, or treated with GSV lipid alone every 24 h for 2 days (UT, untreated cells). Cell number was

measured in the culture wells using a dye binding assay (Experimental protocol). Results are presented as mean ± SD. A one-way ANOVA was performed, followed by a Tukey's multiple comparison test. ▲ indicates a significant difference between cells treated with AON #64 and all of the control treatments ($p < 0.001$).

Figure 31 is a representation showing a reversal of epidermal hyperplasia in psoriatic human skin grafts on nude mice following intradermal injection with antisense oligonucleotides

Grafted psoriasis lesions were injected with IGF-I receptor specific AONs, a random sequence oligonucleotide in PBS, or with PBS alone, every 2 days for 20 days, then analysed histologically. **(a)** Donor A graft treated with AON #50 showing epidermal thinning compared
with pregraft and control *(PBS)* treated graft, and Donor B graft treated with AON #27 showing epidermal thinning compared with pregraft and control (R451) treated graft. E, epidermis; *Scale b*ar, 400 mm; all pictures are at the same magnification. **(b)** Mean epidermal cross-sectional area over the full width of grafts was determined by digital image analysis. Results are presented as mean ± SEM. *Shaded bar*s, control treatments: R451, random oligonucleotide sequence; *solid bar*s, treatments with oligonucleotides that inhibited IGF-I receptor expression in vitro. * indicates a significant difference from the vehicle treated graft ($p < 0.01$, $n = 5\text{-}7$), ++ indicates a significant difference from the random sequence (R451) treated graft ($p < 0.01$, $n = 5\text{-}7$). **(c)** Parakeratosis *(arrow)* was absent in grafts treated with IGF-I receptor AONs *(AON #50)* but persisted in pregraft and control *(PBS)* treated graft. *Scale bar, 100 mm.*

Figure 32 is a representation showing a reversal of epidermal hyperplasia correlates with reduced IGF-I receptor mRNA in grafted psoriasis lesions treated with antisense oligonucleotides (a) A psoriasis lesion prior to grafting, and after grafting and treatment with IGF-I receptor specific oligonucleotide #27 *(AON #27)* or random sequence *(R451)* was immunostained with antibodies to Ki67 to identify proliferating cells. Proliferating cells are

indicated by a dark brown nucleus (arrows). *Scale bar, 250 m*m; all pictures are at the same magnification. **(b)** The same lesion prior to grafting and after oligonucleotide treatment as in (a) was subjected to in situ hybridisation with a ^{35}S-labeled cRNA probe complementary to the human IGF-I receptor mRNA. The presence of IGF-I receptor mRNA is indicated by silver grains (tiny black speckles), which are almost eliminated in the epidermis of the lesion treated with the IGF-I receptor-specific oligonucleotide #27 (AON #27). Arrows indicate the basal layer of the epidermis with dermis underneath. *Scale bar, 50* μm.

Figure 33 is a representation showing a reduction in IGF-I receptor mRNA in HaCaT keratinocytes following treatment with oligonucleotides. HaCaT cell monolayers grown to 90% confluence in DMEM contianing 10% v/v fetal calf serum were treated with 24 h for two days with 2 μg/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Total RNA was isolated and analysed for IGF-I receptor and GAPDH mRNA using a commercially availble ribonuclease protection assay kit (RPAII, Ambicon Inc, Austin, Texas). Band intensity was quantified using ImageQuant software (Molecular Dynamics, Sunnyvale, California).

Figure 34 is a representation showing a reduction in IGF-I receptor protein in HaCaT keratinocytes following treatment with oligonucleotides. HaCaT cell monolayers grown to 90% confluence in DMEM containing 10% v/v fetal calf serum were treated every 24 h for four days with 2 μg/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Cells were lysed in a buffer containing 50 mM HEPES, 150 mM NaCl, 10% v/v gycerol, 1% v/v Triton X-100 and 100 μg/ml aprotinin on ice for 30 mins, then 30 μg of lysate was loaded onto a denaturing 7% w/v polyacrylamide gel followed by transfer onto an Immobilon-P membrane (Millipore, Bedford, Massachusetts). Membranes were incubated with the anti-IGF-I receptor antibody C20 (Sanra Cruz Biotechnology Inc., Santa Cruz, California, 25 ng/ml in 150 mM NaCl, 10 mM Tris-HCl, pH 7.4, 0.1% v/v Tween 20) for 1 h at room temperature and developed using the Vistra ECF western blotting kit (Amersham,

Buckinghamshire, England). Band intensity was quantified using ImageQuant software (Molecular Dynamics, Sunnyvale, California).

Figure 35 is a representation showing a reduction in HaCaT keratinocyte cell number following treatment with oligonucleotides. HaCaT cell monolayers grown to 40% confluence in DMEM containing 10% fetal calf serum were treated every 24 h for three days with 2 μg/ml GSV·lipid alone (GSV) or complexed with 15 nM oligonucleotide. Cell number was measured every 24 h using the amido black dye binding assay [32].

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is predicated in part on the use of molecules and in particular genetic molecules and more particularly antisense molecules to down-regulate a growth factor, its receptor and/or growth factor expression facilitating sequences.

Accordingly, one aspect of the present invention contemplates a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation or a cell otherwise involved in the said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing a growth factor mediated cell proliferation and/or inflammation and/or other medical disorder.

Growth factor mediated cell proliferation and inflammation are also referred to as epidermal hyperplasias and these and other medical disorders may be mediated by any number of molecules such as but not limited to IGF-I, keratinocyte growth factor (KGF), transforming growth factor-α (TGFα), tumour necrosis factor-α (TNFα), interleukin-1, -4, -6 and 8 (IL-1, IL-4, IL-6 and IL-8, respectively), basic fibroblast growth factor (bFGF) or a combination of one or more of the above. The present invention is particularly described and exemplified with reference to IGF-I and its receptor (IGF-I receptor) and to IGF-I facilitating molecules, IGFBPs, since targeting these molecules according to the methods contemplated herein provides the best results to date. This is done, however, with the understanding that the present invention extends to any growth factor or cytokine-like molecule, a receptor thereof or a facilitating molecule like the IGFBPs involved in skin cell proliferation such as those molecules contemplated above and/or their receptors and/or facilitating molecules therefor.

According to this preferred embodiment, there is provided a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a

mammal, said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation or a cell otherwise involved with said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation and/or other medical disorder.

The present invention is particularly described by psoriasis as the proliferative skin disorder. However, the subject invention extends to a range of proliferative and/or inflammatory skin disorders or epidermal hyperplasias such as but not limited to psoriasis, ichthyosis, pityriasis rubra pilaris ("PRP"), seborrhoea, keloids, keratoses, neoplasias and scleroderma, warts, benign growths and cancers of the skin. The present invention extends to a range of other disorders such as neovascularization conditions such as but not limited to hyperneovasularization such as neovascularization of the retina, lining of the brain, skin, hyperproliferation of the inside of blood vessels, kidney disease, atherosclerotic disease, hyperplasias of the gut epithelium or growth factor mediated malignancies such as IGF1-mediated malignancies.

Furthermore, down-regulation of IGF-I receptor is useful as adjunctive therapy for epidermal hyperplasia. In accordance with this aspect of the present invention it is known that IGF-I receptor elicits separate intracellular signals which prevent apoptosis [19]. In keratinocytes, IGF-I receptor activation has been shown to protect UV-irradiated cells from apoptosis [20]. In another cell type, a number of IGF-I receptors expressed by the cells correlated with tumorigenicity and apoptotic resistance [21]. Consequently, in accordance with the present invention, by inactivating IGF-I receptor on cells such as epidermal keratinocytes will achieve three important outcomes:

(i) Acute epidermal hyperplasia following UV has been suggested to increase the risk of keratinocyte carcinogenic transformation [22]. By reducing IGF-I receptor expression in the epidermis, the incidence of epidermal hyperplasia following UV exposure is

likely to be reduced leading to an overall acceleration in normalization of the lesion and reduced carcinogenic risk.

(ii) Inhibition of anti-apoptotic action of IGF-I receptor will enhance the reversal of epidermal thickening and accelerate normalization of differentiation. Topical or injected IGF-I receptor antisense as adjunctive treatment will increase apoptosis in the epidermal layer thereby enhancing the reduction in acanthosis observed in UV treatments.

(iii) Survival of keratinocytes, ie. those which evade apoptosis is likely to occur when cells have damaged DNA. Such mutations may be in the tumor suppressor region. Consequently, the use of antisense therapy will result in less frequent selection of mutated keratinocytes and therefore reduced incidence of basal cell carcinomas and squamous.

According to this embodiment, there is provided a method for ameliorating the effects of a proliferative and/or inflammatory skin disorder such as psoriasis said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation with effective amounts of UV treatment and a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation.

The UV treatment and nucleic acid molecule or its chemical analogue may be administered in any order or may be done simultaneously. This method is particularly useful in treating psoriasis by combination of UV and antisense therapy. Preferably the antisense therapy is directed to the IGF-I receptor.

In a preferred embodiment, the present invention is directed to a method for ameliorating the effects of psoriasis or other medical disorder, said method comprising contacting proliferating

skin or skin capable of proliferation or cells associated with said disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation or ameliorating the medical disorder.

The present invention extends to any mammal such as but not limited to humans, livestock animals (e.g. horses, sheep, cows, goats, pigs, donkeys), laboratory test animals (e.g. rabbits, mice, guinea pigs), companion animals (e.g. cats, dogs) and captive wild animals. However, the instant invention is particularly directed to proliferative and/or inflammatory skin disorders such as psoriasis in humans as well as medical disorders contemplated above.

The aspects of the subject invention instantly contemplated are particularly directed to the topical application of one or more suitable nucleic molecules capable of inhibiting, reducing or otherwise interfering with IGF-mediated cell proliferation and/or inflammation. More particularly, the nucleic acid molecule targets IGF-I interaction with its receptor. Conveniently, therefore, the nucleic acid molecule is an antagonist of IGF-I interaction with its receptor. Most conveniently, the nucleic acid molecule antagonist is an antisense molecule to the IGF-I receptor, to IGF-I itself or to a molecule capable of facilitating IGF-I interaction with its receptor such as but not limited to an IGFBP.

Insofar as the invention relates to IGFBPs, the preferred molecules are IGFBP-2, -3, -4, -5 and -6. The most preferred molecules are IGFBP-2 and IGFBP-3.

The nucleotide sequences of IGFBP-2 and IGFBP-3 are set forth in Figures 1 ~~(<400>1)~~ and 2 ~~(<400>2)~~, respectively. According to a particularly preferred aspect of the present invention, there is provided a nucleic acid molecule comprising at least about ten nucleotides capable of hybridising to, forming a heteroduplex or otherwise interacting with an mRNA molecule directed from a gene corresponding to a genomic form of ~~<400>1 and/or <400>2~~ SEQ ID NO. 1 and/or SEQ ID NO. 2 and which thereby reduces or inhibits translation of said mRNA molecule. Preferably, the nucleic acid molecule is at least about 15 nucleotides in length and more

preferably at least about 20-25 nucleotides in length. However, the instant invention extends to any length nucleic acid molecule including a molecule of 100-200 nucleotides in length to correspond to the full length of or near full length of the subject genes.

The nucleotide sequence of the antisense molecules may correspond exactly to a region or portion of ~~<400>1 or <400>2~~ SEQ ID NO. 1 or SEQ ID NO. 2 or may differ by one or more nucleotide substitutions, deletions and/or additions. It is a requirement, however, that the nucleic acid molecule interact with an mRNA molecule to thereby reduce its translation into active protein.

Examples of potential antisense molecules for IGFBP-2 and IGFBP-3 are those capable of interacting with sequences selected from the lists in Examples 6 and 7, respectively.

The nucleic acid molecules in the form of an antisense molecule may be linear or covalently closed circular and single stranded or partially double stranded. A double stranded molecule may form a triplex with target mRNA or a target gene. The molecule may also be protected from, for example, nucleases, by any number of means such as using a nonionic backbone or a phosphorothioate linkage. A convenient nonionic backbone contemplated herein is ethylphosphotriester linkage or a 2'-O-methylribosyl derivative. A particularly useful modification modifies the DNA backbone by introducing phosphorothioate internucleotide linkages. Alternatively or in addition to the pyrimidine bases are modified by inclusion of a C-5 propyne substitution which modification is proposed to enhance duplex stability [23]. The present invention extends to any chemical modification to the bases and/or RNA or DNA backbone. Reference to a "chemical analogue" of a nucleic acid molecule includes reference to a modified base, nucleotide, nucleoside or phosphate backbone.

Examples of suitable oligonucleotide analogues are conveniently described in Ts'O *et al* [7]. Further suitable examples of oligonucleotide analogues and chemical modifications are described in references 25 to 31.

Alternatively, the antisense molecules of the present invention may target the IGF-I gene itself or its receptor or a multivalent antisense molecule may be constructed or separate molecules administered which target at least two or an IGFBP, IGF-I and/or IGF-I-receptor. Examples of suitable antisense molecules capable of targetting the IGF-I receptor are those capable of interacting with sequences selected from the list in Example 8. One particularly useful antisense molecule is 5'- ATCTCTCCGCTTCCTTTC -3' ~~(<400>10).~~ (SEQ ID NO.10)

Other particularly useful antisense molecules are:

#27 UCCGGAGCCAGACUU^ (SEQ ID NO.12)

#64 CACAGUUGCUGCAAG^ (SEQ ID NO.13)

#78 UCUCCGCUUCCUUUC^ (SEQ ID NO.14)

#28 AGCCCCCACAGCGAG^ (SEQ ID NO.15)

#32 GCCUUGGAGAUGAGC^ (SEQ ID NO.16)

#40 UAACAGAGGUCAGCA^ (SEQ ID NO.17)

#42 GGAUCAGGGACCAGU^ (SEQ ID NO.18)

#46 CGGCAAGCUACACAG^ (SEQ ID NO.19)

#50 GGCAGGCAGGCACAC^ (SEQ ID NO.20)

Particularly useful molecules are selected from #27, #64 and #78. In a preferred embodiment these molecules comprise a C-5 propynyl dU, dC phosphorothioate modification.

A particularly preferred embodiment of the present invention contemplates a method of ameliorating the effects of psoriasis or other medical disorder, said method comprising contacting proliferating skin or skin capable of proliferation or cells associated with said medical disorder with an effective amount of one or more nucleic acid molecules or chemical analogues thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation or ameliorating the medical disorder wherein said one or more molecules comprises a polynucleotide capable of interacting with mRNA directed from an IGF-I gene, an IGF-I receptor gene or a gene encoding an IGFBP such as IGFBP-2 and/or IGFBP-3.

Preferably, the nucleic acid molecule are antisense molecules. Particularly useful antisense molecules ~~are~~: May be represented as

#27 UCCGGAGCCAGACUU^ (SEQ ID NO.12)

#64 CACAGUUGCUGCAAG^ (SEQ ID NO.13)

#78 UCUCCGCUUCCUUUC^ (SEQ ID NO.14)

#28 AGCCCCCACAGCGAG^ (SEQ ID NO. 15)

#32 GCCUUGGAGAUGAGC^ (SEQ ID NO.16)

#40 UAACAGAGGUCAGCA^ (SEQ ID NO.17)

#42 GGAUCAGGGACCAGU^ (SEQ ID NO.18)

#46 CGGCAAGCUACACAG^ (SEQ ID NO.19)

#50 GGCAGGCAGGCACAC^ (SEQ ID NO.20)

Even more particularly useful molecules are selected from #27, #64 and #78.

In accordance with one aspect of the present invention the nucleic acid molecule is topically applied in aqueous solution or in conjunction with a cream, ointment, oil or other suitable carrier and/or diluent. A single application may be sufficient depending on the severity or exigencies of the condition although more commonly, multiple applications are required ranging from hourly, multi-hourly, daily, multi-daily, weekly or monthly, or in some other suitable time interval. The treatment might comprise solely the application of the nucleic acid molecule or this may be applied in conjunction with other treatments for the skin proliferation and/or inflammatory disorder being treated or for other associated conditions including microbial infection, bleeding and the formation of a variety of rashes.

As an alternative to or in conjunction with antisense therapy, the subject invention extends to the nucleic acid molecule as, or incorporating, a ribozyme including a minizyme to, for example, IGF-I, its receptor or to molecules such as IGFBPs and in particular IGFBP-2 and -3. Ribozymes are synthetic nucleic acid molecules which possess highly specific endoribonuclease activity. In particular, they comprise a hybridising region which is complementary in nucleotide

sequence to at least part of a target RNA. Ribozymes are well described by Haseloff and Gerlach [8] and in International Patent Application No. WO 89/05852. The present invention extends to ribozymes which target mRNA specified by genes encoding IGF-I, its receptor or one or more IGFBPs such as IGFBP-2 and/or IGFBP-3.

According to this embodiment, there is provided in a particularly preferred aspect a ribozyme comprising a hybridising region and a catalytic region wherein the hybridising region is capable of hybridising to at least part of a target mRNA sequence transcribed from a genomic gene corresponding to ~~(<400>1) or (<400>2)~~ SEQ ID NO.1 or SEQ ID NO.2 wherein said catalytic domain is capable of cleaving said target mRNA sequence to reduce or inhibit IGF-I mediated cell proliferation and/or inflammation and/or other medical disorders.

Yet another aspect of the present invention contemplates co-suppression to reduce expression or to inhibit translation of an endogenous gene encoding, for example, IGF-I, its receptor, or IGFBPs such as IGFBP-2 and/or -3. In co-suppression, a second copy of an endogenous gene or a substantially similar copy or analogue of an endogenous gene is introduced into a cell following topical administration. As with antisense molecules, nucleic acid molecules defining a ribozyme or nucleic acid molecules useful in co-suppression may first be protected such as by using a nonionic backbone.

The efficacy of the nucleic acid molecules of the present invention can be conveniently tested and screened using an *in vitro* system comprising a basal keratinocyte cell line. A particularly useful system comprises the HaCaT cell line described by Boukamp *et al* [9]. In one assay, IGF-I is added to an oligonucleotide treated HaCaT cell line. Alternatively, growth of oligonucleotide treated HaCaT cells is observed on a feeder layer of irradiated 3T3 fibroblasts. Using such *in vitro* assays, it is observed that antisense oligonucleotides to IGFBP-3, for example, inhibit production of IGFBP-3 by HaCaT cells. Other suitable animal models include the nude mouse/human skin graft model (15; 16) and the "flaky skin" mouse model (17; 18). In the nude mouse model, microdermatome biopsies of psoriasis lesions are taken under

local anaesthetic from volunteers then transplanted to congenital athymic (nude) mice. These transplanted human skin grafts maintain the characteristic hyperproliferating epidermis for 6-8 weeks. They are an established model for testing the efficacy of topically applied therapies for psoriasis. In the "flaky skin" mouse model, the fsn/fsn mutation produces mice with skin resembling human psoriasis. This mouse, or another mutant mouse with a similar phenotype is a further *in vivo* model to test the efficacy of topically applied therapies for psoriasis.

Another aspect of the present invention contemplates a pharmaceutical composition for topical administration which comprises a nucleic acid molecule capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation such as psoriasis and one or more pharmaceutically acceptable carriers and/or diluents. Preferably, the nucleic acid molecule is an antisense molecule to IGF-I, the IGF-I receptor or an IGFBP such as IGFBP-2 and/or IGFBP-3 or comprises a ribozyme to one or more of these targets or is a molecule suitable for co-suppression of one or more of these targets. The composition may comprise a single species of a nucleic acid molecule capable of targeting one of IGF-I, its receptor or an IGFBP, such as IGFBP-2 or IGFBP-3 or may be a multi-valent molecule capable of targeting two or more of IGF-I, its receptor or an IGFBP, such as IGFBP-2 and/or IGFBP-3.

The nucleic acid molecules may be administered in dispersions prepared in creams, ointments, oil or other suitable carrier and/or diluent such as glycerol, liquid polyethylene glycols and/or mixtures thereof. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for topical use include sterile aqueous solutions (where water soluble) or dispersions and powders for the extemporaneous preparation of topical solutions or dispersions. In all cases, the form is preferably sterile although this is not an absolute requirement and is stable under the conditions of manufacture and storage. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures

thereof and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of superfactants. The prevention of the action of microorganism can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride.

Topical solutions are prepared by incorporating the nucleic acid molecule compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by where necessary filter sterilization.

The active agent may alternatively be administered by intravenous, subcutaneous, nasal drip, suppository, implant means amongst other suitable routes of administration including intraperitoneal, intramuscular, absorption through epithelial or mucocutaneous linings for example via nasal, oral, vaginal, rectal or gastrointestinal administration. Reference may conveniently be made to reference 24.

As used herein "pharmaceutically acceptable carriers and/or diluents" include any and all solvents, dispersion media, aqueous solutions, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, use thereof in the pharmaceutical compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. Conveniently, the nucleic acid molecules of the present invention are stored in freeze-dried form and are reconstituted prior to use.

Yet another aspect of the present invention contemplates the use of a nucleic acid molecule in the manufacture of a medicament for the treatment of proliferative and/or inflammatory skin disorders or other medical disorders mediated by a growth factor. The proliferative and/or

inflammatory skin disorder is generally psoriasis or other medical disorders as described above and the nucleic acid molecule targets IGF-I, the IGF-I receptor and/or an IGFBP such as IGFBP-2 and/or IGFBP-3.

Still a further aspect of the present invention contemplates an agent comprising a nucleic acid molecule as hereinbefore defined useful in the treatment of proliferative and/or inflammatory skin disorders, such as psoriasis or other medical disorder..

The present invention further contemplates the use of the genetic molecules and in particular the antisense molecules to inhibit the anti-apoptotic activity of IGF-I receptor. Such a use is appropriate for the treatment of certain cancers and as adjunct therapy for epidermal hyperplasia such as in combination with UV treatment.

The present invention is further described by the following non-limiting Examples.

EXAMPLE 1

The differentiated human keratinocyte cell line, HaCaT [9] was used in the *in vitro* assay. Cells at passage numbers 33 to 36 were maintained as monolayer cultures in 5% v/v CO_2 at 37°C in Keratinocyte-SFM (Gibco) containing EGF and bovine pituitary extract as supplied. Media containing foetal calf serum were avoided because of the high content of IGF-I binding proteins in serum.

Feeder layer plates of lethally irradiated 3T3 fibroblasts were prepared exactly as described by Rheinwald and Green [10].

EXAMPLE 2

Cells were grown to 4 days post confluence in $2cm^2$ wells with daily medium changes of Keratinocyte-SFM, then the medium was changed to DMEM (Cytosystems, Australia), with the following additions: 25mM Hepes, 0.19% w/v, sodium bicarbonate, 0.03% w/v glutamine (Sigma Chemical Co, USA), 50IU/ml penicillin and 50µg/ml streptomycin (Flow Laboratories). After 24 hours, IGF-I or tIGF-I was added to triplicate wells, at the concentrations indicated, in 0.5ml fresh DMEM containing 0.02% v/v bovine serum albumin (Sigma molecular biology grade) and incubated for a further 21 hours. [^{3}H]-Thymidine (0.1µCi/well) was then added and the cells incubated for a further 3 hours. The medium was then aspirated and the cells washed once with ice-cold PBS and twice with ice-cold 10% v/v TCA. The TCA-precipitated monolayers were then solubilized with 0.25M NaOH (200µl/well), transferred to scintillation vials and radioactivity determined by liquid scintillation counting (Pharmacia Wallac 1410 liquid scintillation counter).

EXAMPLE 3

HaCaT conditioned medium (250µl) was concentrated by adding 750µl cold ethanol, incubating at -20°C for 2 hours and centrifuging at 16,000g for 20 min at 4°C. The resulting pellet was air dried, resuspended thoroughly in non-reducing Laemmli sample buffer, heated to 90°C for 5 minutes and separated on 12% w/v SDS-PAGE according to the method of Laemmli (1970).

Separated proteins were electrophoretically transferred to nitrocellulose membrane (0.45mm, Schleicher and Schuell, Dassel, Germany) in a buffer containing 25mM Tris, 192mM glycine and 20% v/v methanol. IGFBPs were then visualised by the procedure of Hossenlopp *et al* [11], using [^{125}I]-IGF-I, followed by autoradiography. Autoradiographs were scanned in a BioRad Model GS-670 Imaging Densitometer and band densities were determined using the Molecular Analyst program.

EXAMPLE 4

Phosphorothioate oligodeoxynucleotides were synthesised by Bresatec, Adelaide, South Australia, Australia. The following antisense sequences were used: BP3AS2, 5'- GCG CCC GCT GCA TGA CGC CTG CAA C -3' (SEQ ID NO. 4) ~~(<400>4)~~, a 25mer complementary to the start codon region of the human IGFBP-3 mRNA; BP3AS3, 5'- CGG GCG GCT CAC CTG GAG CTG GCG -3' (SEQ ID NO. 5) ~~(<400>5)~~, a 24mer complementary to the exon 1/intron 1 splice site; BP3AS4, 5'- AGG CGG CTG ACG GCA CTA -3' (SEQ ID NO. 6) ~~(<400>6)~~, an 18mer complementary to a region of the coding sequence lacking RNA secondary structure and oligonucleotide-dimer formation (using the computer software "OLIGO for PC"). Since BP3AS4 was found to be ineffective at inhibiting IGFBP-3 synthesis, it was used as a control. The following additional control oligonucleotide sequences were used: BP3S, 5'- CAG GCG TCA TGC AGC GGG C -3' (SEQ ID NO. 7) ~~(<400>7)~~, an 18mer sense control sequence equivalent to the start codon region; BP3AS2NS, 5'- CGG AGA TGC CGC ATG CCA GCG CAG G -3' (SEQ ID NO. 8) ~~(<400>8)~~, a 25mer randomised sequence with the same GC content as BP3AS2; BP3AS4NS, 5'- GAC AGC GTC GGA GCG ATC -3' (SEQ ID NO. 9) ~~(<400>9)~~, an 18mer randomised sequence with the same GC content as BP3AS4NS. Design of the oligonucleotides was based on the human IGFBP-3 cDNA sequence of Spratt *et al* [12].

Cells were grown to one day post confluence in 2cm^2 wells with daily medium changes of 0.5ml Keratinocyte-SFM, then subjected to daily medium changes of Keratinocyte-SFM for a further 4 days. Daily additions of 0.5ml fresh Keratinocyte-SFM were then continued for a further 7 days, except that at the time of medium addition, 5µl oligonucleotide in PBS was added to give

the final concentrations indicated, then the wells were shaken to mix the oligonucleotide. After the final addition, cells were incubated for 24 hours and the medium collected for assay of IGFBPs. Cells were then counted after trypsinisation in a Coulter Industrial D Counter, Coulter Bedfordshire, UK. Cell numbers after oligonucleotide treatment differed by less than 10%.

EXAMPLE 5

HaCaT cells secrete mainly IGFBP-3 (>95%), with the only other IGFBP detectable in HaCaT conditioned medium being IGFBP-4 (<5%). The effect on IGFBP-3 and IGFBP-4 synthesis of antisense oligonucleotides at two concentrations, 5μM and 0.5μM, was tested. Two oligonucleotides were used, BP3AS2 and BP3AS3, directed against the start site and the intron 1/exon 1 splice site, respectively of the IGFBP-3 mRNA. As a control, a sense oligonucleotide corresponding to the start site was used. As shown in Figures 4A and 4B, all oligonucleotides at 5μM caused a significant reduction of IGFBP-3 synthesis compared with untreated cells, however, the two antisense oligonucleotides inhibited IGFBP-3 synthesis of approximately 50% compared to the sense control (Figure 4B). The antisense oligonucleotide directed to the start codon appeared to be more effective of the two, the difference being more apparent at the lower concentration of 0.5μM. The cells of IGFBP-4 secreted by the HaCaT cells make photographic reproduction of the bands on Western ligand blots difficult, however densitometry measurements provide adequate relative quantitation. This resulted in the significant observation that IGFBP-4 levels were unaffected by oligonucleotide addition to the cells, suggesting that the observed inhibitory effects on IGFBP-3 are specific.

To further investigate the inhibitory effects of the more effective of the two antisense oligonucleotides, BP3AS2, inhibition by this oligonucleotide at 0.5μM was compared with a number of control oligonucleotides, including one antisense oligonucleotide to IGFBP-3 that had proved to be ineffective at 0.5μM. As shown in Figures 5A and 5B, BP3AS2 was again inhibitory, resulting in levels of IGFBP-3 of approximately 50% of the most non-specifically inhibitory control oligonucleotide, the randomised equivalent of BP3AS2. The other control oligonucleotides caused no reduction in IGFBP-3 levels at 0.5μM, compared to untreated cells.

Of possible significance is the fact that this control oligonucleotide, BP3AS2NS, like BP3AS2 itself, has the highest potential T_m of the three control oligonucleotides used in this experiment, enhancing the probability of non-specific base pairing with non-target mRNAs. However, the lack of inhibition of IGFBP-4 secretion by BP3AS2 suggests that this oligonucleotide is selective even compared with the most closely related protein likely to be present in this cell line.

EXAMPLE 6

Antisense oligonucleotides to IGFBP2 may be selected from molecules capable of interacting with one or more ~~of the following sense oligonucleotides:~~

ATTCGGGGCGAGGGA	AGGAGGCGGCTCCCG	CACCTGCCCGCCCGC
TTCGGGGCGAGGGAG	GGAGGCGGCTCCCGC	ACCTGCCCGCCCGCC
TCGGGGCGAGGGAGG	GAGGCGGCTCCCGCT	CCTGCCCGCCCGCCC
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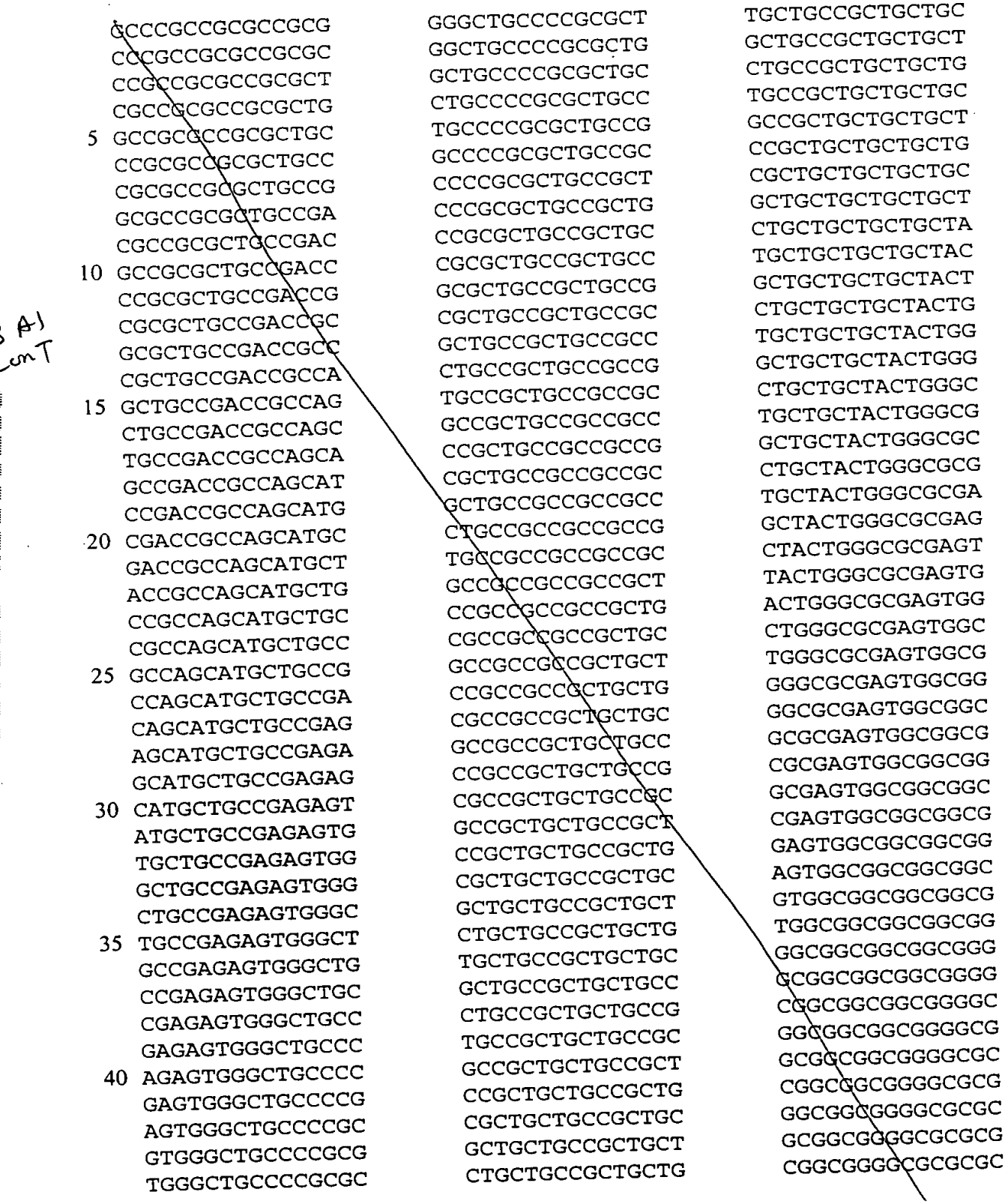

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SUB A1
CmT

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SUB A1 CONT

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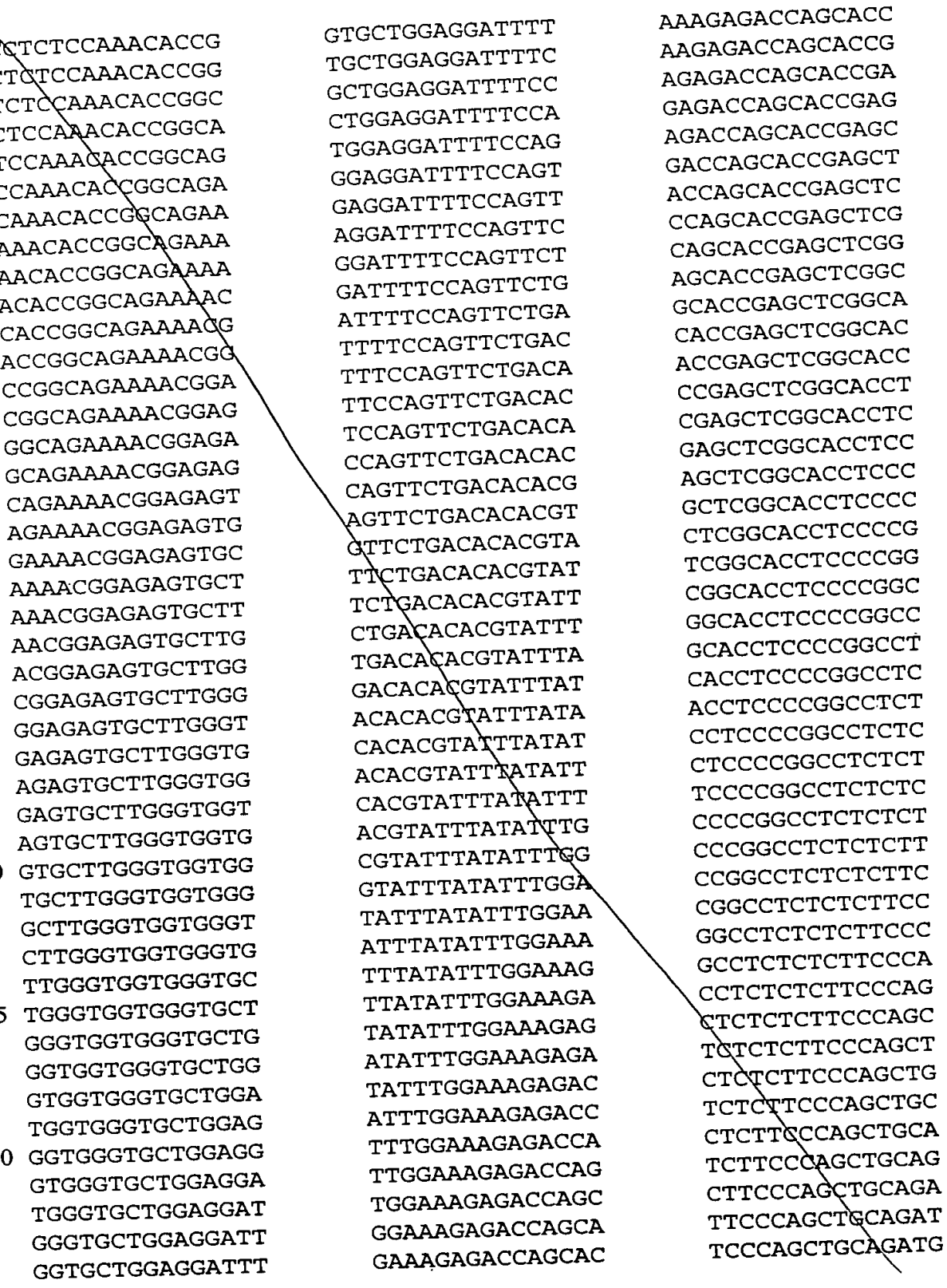
SUB A1
cont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AACACCGGCAGAAAA
ACACCGGCAGAAAAC
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GGCAGAAAACGGAGA
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TCTCTTCCCAGCTGC
CTCTTCCCAGCTGCA
TCTTCCCAGCTGCAG
CTTCCCAGCTGCAGA
TTCCCAGCTGCAGAT
TCCCAGCTGCAGATG

SUB A1
CONT

CCCAGCTGCAGATGC
CCAGCTGCAGATGCC
CAGCTGCAGATGCCA
AGCTGCAGATGCCAC
GCTGCAGATGCCACA
CTGCAGATGCCACAC
TGCAGATGCCACACC
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GAAGGGGGTTGTGGT
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SUB A1 cont

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CATAAGATTAAAGGA
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EXAMPLE 7

Antisense oligonucleotides to IGFBP3 may be selected from molecules capable of interacting with one or more ~~of the following sense oligonucleotides:~~

SUB A2

CTCAGCGCCCAGCCG
TCAGCGCCCAGCCGC
CAGCGCCCAGCCGCT
AGCGCCCAGCCGCTT
GCGCCCAGCCGCTTC
CGCCCAGCCGCTTCC
GCCCAGCCGCTTCCT
CCCAGCCGCTTCCTG
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AGCCGCTTCCTGCCT
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GCCTGGATTCCACAG
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SUB A2 Gma

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CGGTTGCAGGCGTCA
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SUB A2 CONT

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SUBAZ CONT

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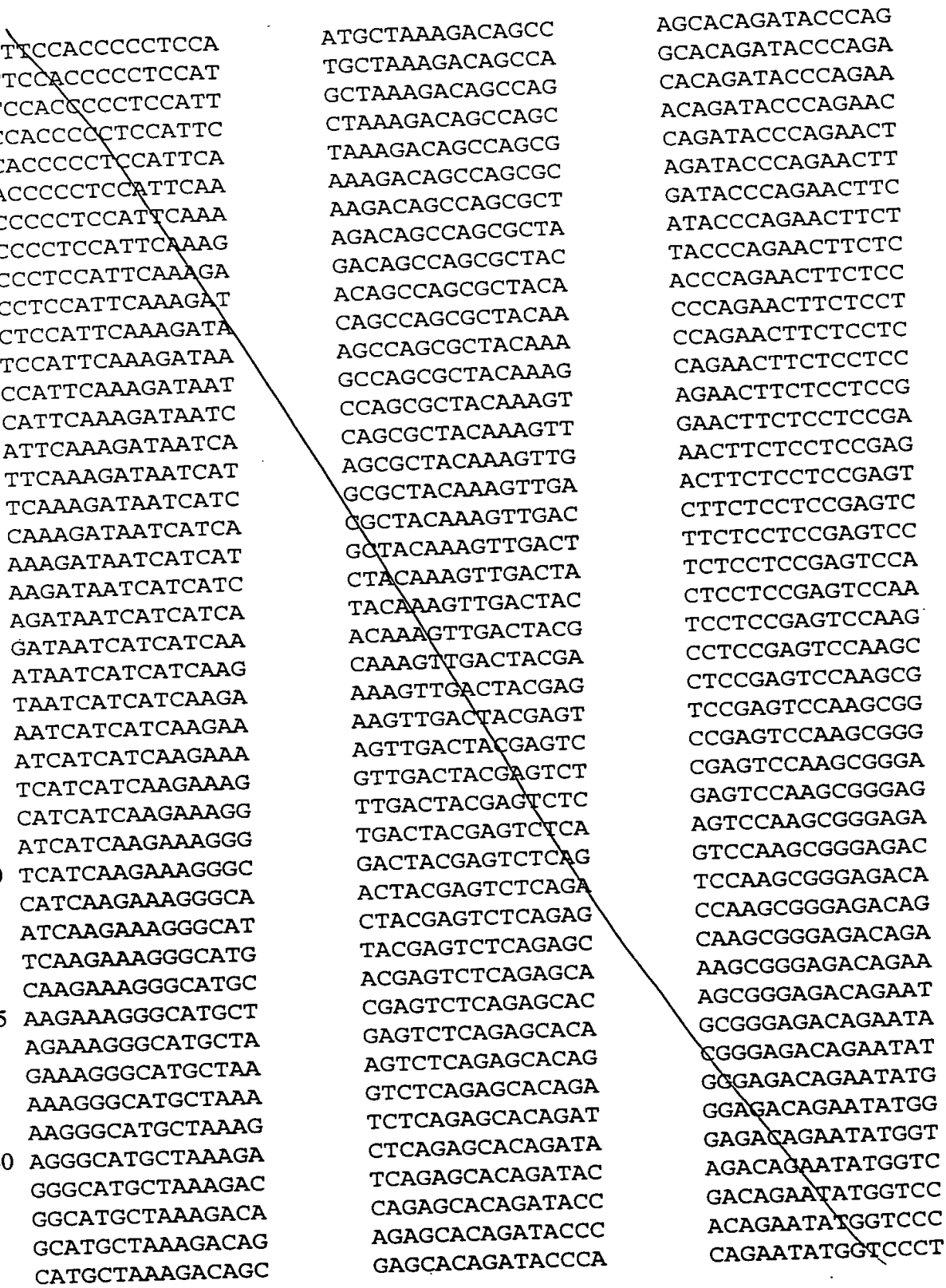
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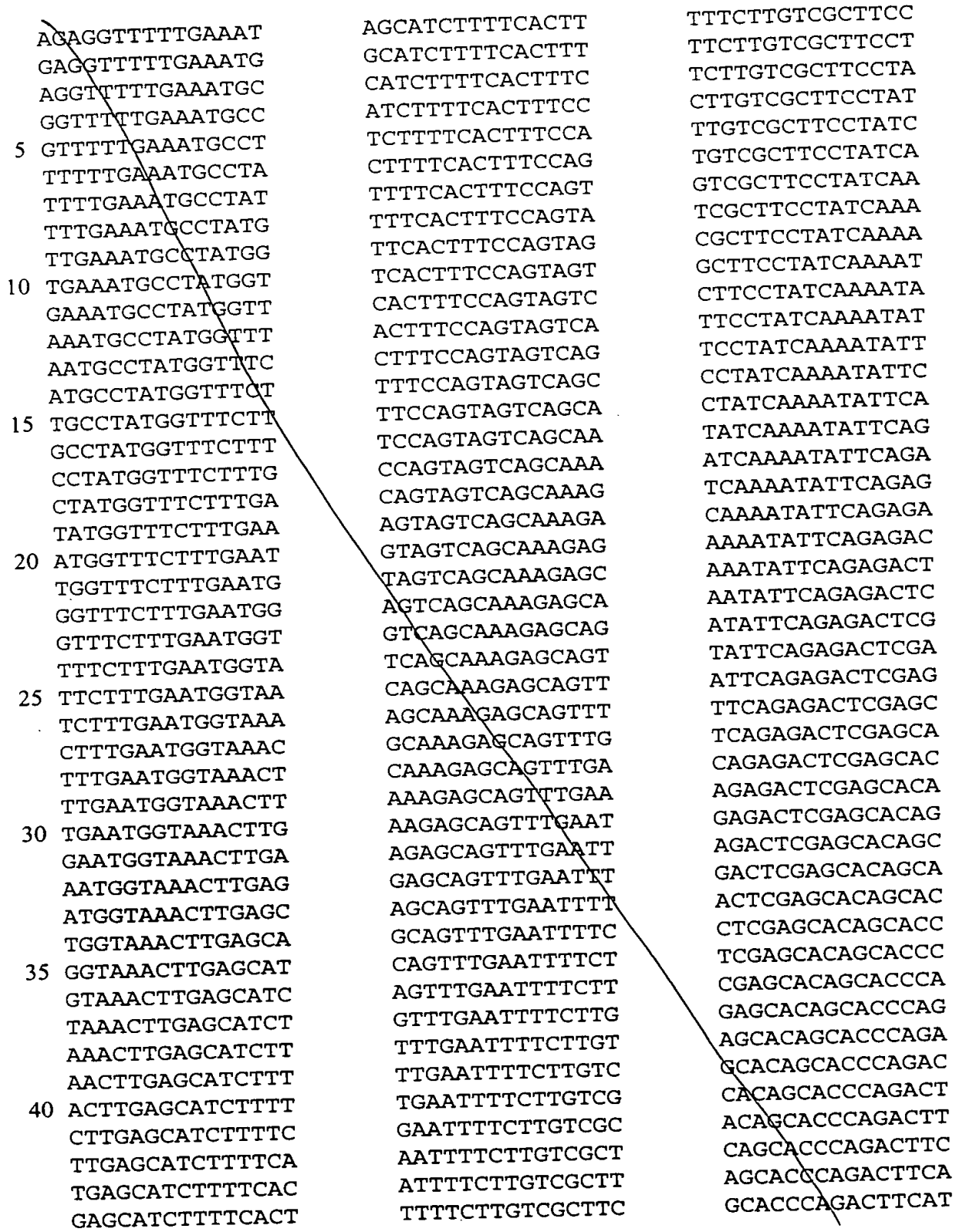
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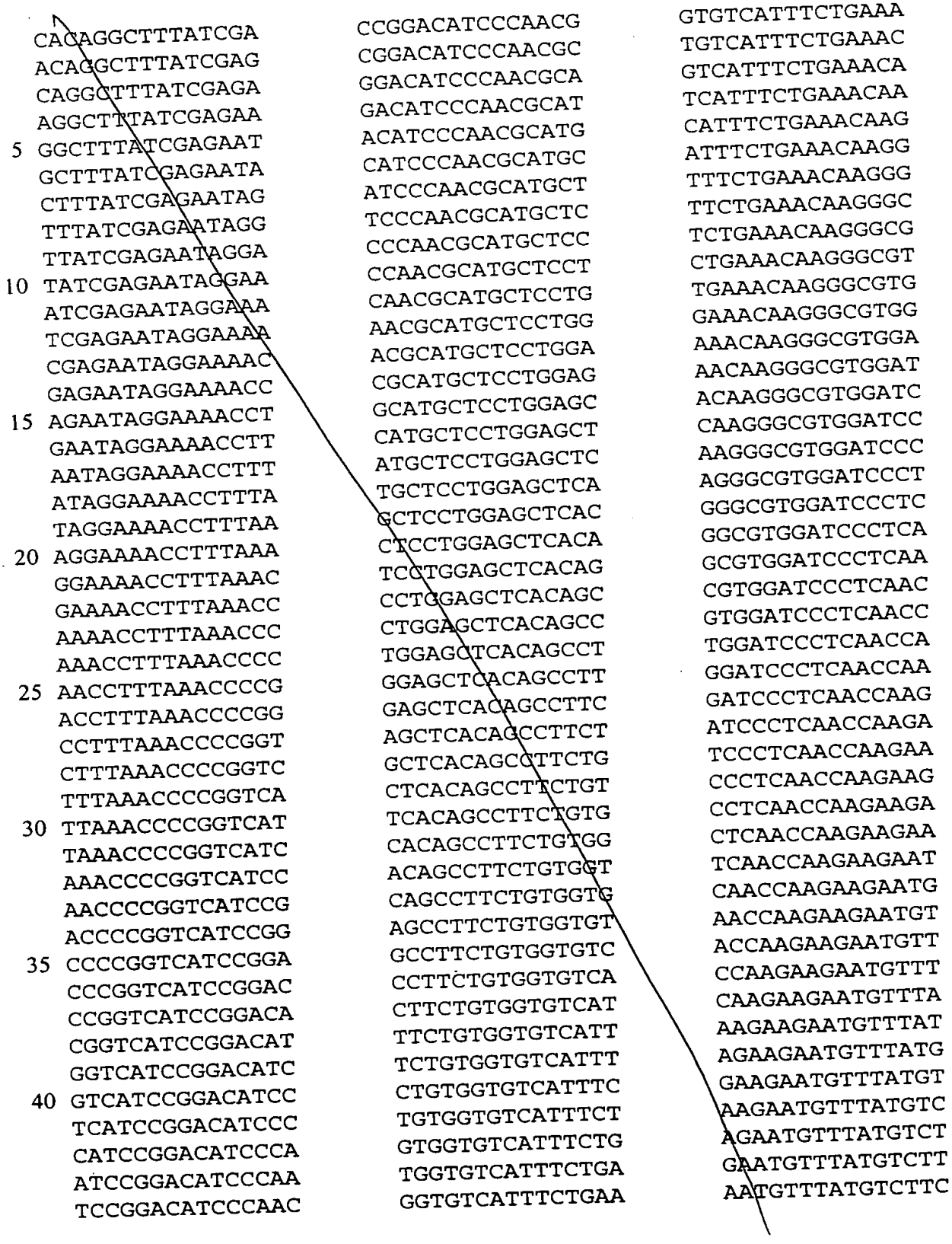
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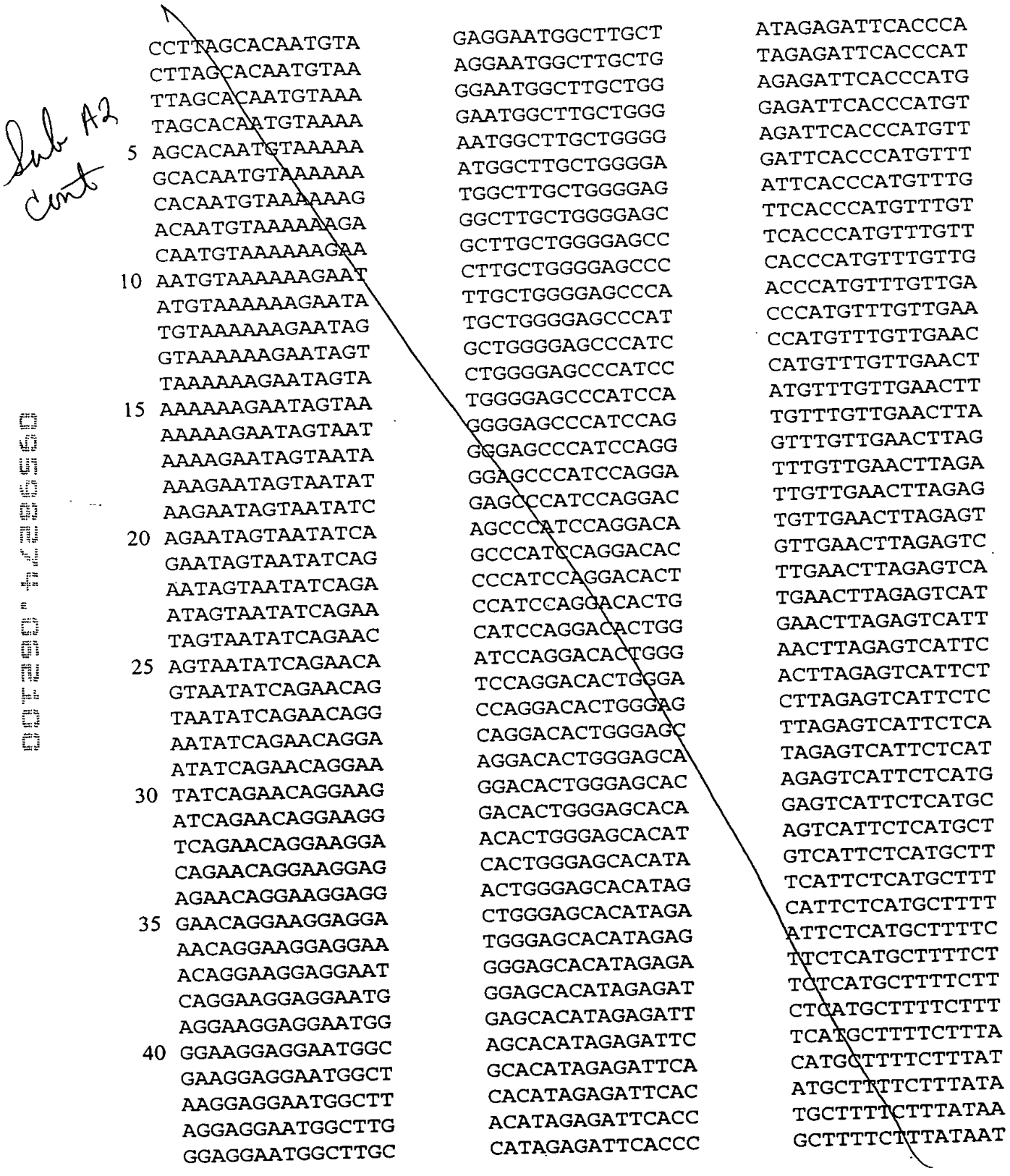
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ACATATATGCAGAGA	CATAGCCCCAAATAT	GAAATGTTAGAGATG
CATATATGCAGAGAA	ATAGCCCCAAATATA	AAATGTTAGAGATGC
ATATATGCAGAGAAG	TAGCCCCAAATATAG	AATGTTAGAGATGCT
TATATGCAGAGAAGA	AGCCCCAAATATAGT	ATGTTAGAGATGCTA
ATATGCAGAGAAGAT	GCCCCAAATATAGTA	TGTTAGAGATGCTAT
TATGCAGAGAAGATA	CCCCAAATATAGTAA	GTTAGAGATGCTATA
ATGCAGAGAAGATAT	CCCAAATATAGTAAG	TTAGAGATGCTATAT
TGCAGAGAAGATATG	CCAAATATAGTAAGA	TAGAGATGCTATATG
GCAGAGAAGATATGT	CAAATATAGTAAGAT	AGAGATGCTATATGA
CAGAGAAGATATGTT	AAATATAGTAAGATC	GAGATGCTATATGAT
AGAGAAGATATGTTC	AATATAGTAAGATCT	AGATGCTATATGATA
GAGAAGATATGTTCT	ATATAGTAAGATCTA	GATGCTATATGATAC
AGAAGATATGTTCTT	TATAGTAAGATCTAT	ATGCTATATGATACA
GAAGATATGTTCTTG	ATAGTAAGATCTATA	TGCTATATGATACAA
AAGATATGTTCTTGT	TAGTAAGATCTATAC	GCTATATGATACAAC
AGATATGTTCTTGTT	AGTAAGATCTATACT	CTATATGATACAACT
GATATGTTCTTGTTA	GTAAGATCTATACTA	TATATGATACAACTG
ATATGTTCTTGTTAA	TAAGATCTATACTAG	ATATGATACAACTGT
TATGTTCTTGTTAAC	AAGATCTATACTAGA	TATGATACAACTGTG
ATGTTCTTGTTAACA	AGATCTATACTAGAT	ATGATACAACTGTGG
TGTTCTTGTTAACAT	GATCTATACTAGATA	TGATACAACTGTGGC
GTTCTTGTTAACATT	ATCTATACTAGATAA	GATACAACTGTGGCC
TTCTTGTTAACATTG	TCTATACTAGATAAT	ATACAACTGTGGCCA
TCTTGTTAACATTGT	CTATACTAGATAATC	TACAACTGTGGCCAT
CTTGTTAACATTGTA	TATACTAGATAATCC	ACAACTGTGGCCATG
TTGTTAACATTGTAT	ATACTAGATAATCCT	CAACTGTGGCCATGA

Sub A2 cont

AACTGTGGCCATGAC
ACTGTGGCCATGACT
CTGTGGCCATGACTG
TGTGGCCATGACTGA
GTGGCCATGACTGAG
TGGCCATGACTGAGG
GGCCATGACTGAGGA
GCCATGACTGAGGAA
CCATGACTGAGGAAA
CATGACTGAGGAAAG
ATGACTGAGGAAAGG
TGACTGAGGAAAGGA
GACTGAGGAAAGGAG
ACTGAGGAAAGGAGC
CTGAGGAAAGGAGCT
TGAGGAAAGGAGCTC
GAGGAAAGGAGCTCA
AGGAAAGGAGCTCAC
GGAAAGGAGCTCACG
GAAAGGAGCTCACGC
AAAGGAGCTCACGCC
AAGGAGCTCACGCCC
AGGAGCTCACGCCCA
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GAGCTCACGCCCAGA
AGCTCACGCCCAGAG
GCTCACGCCCAGAGA
CTCACGCCCAGAGAC
TCACGCCCAGAGACT
CACGCCCAGAGACTG
ACGCCCAGAGACTGG
CGCCCAGAGACTGGG
GCCCAGAGACTGGGC
CCCAGAGACTGGGCT
CCAGAGACTGGGCTG
CAGAGACTGGGCTGC
AGAGACTGGGCTGCT
GAGACTGGGCTGCTC
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GACTGGGCTGCTCTC
ACTGGGCTGCTCTCC
CTGGGCTGCTCTCCC
TGGGCTGCTCTCCCG
GGGCTGCTCTCCCGG

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GCTGCTCTCCCGGAG
CTGCTCTCCCGGAGG
TGCTCTCCCGGAGGC
GCTCTCCCGGAGGCC
CTCTCCCGGAGGCCA
TCTCCCGGAGGCCAA
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GGCCAAACCCAAGAA
GCCAAACCCAAGAAG
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CAAACCCAAGAAGGT
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AACCCAAGAAGGTCT
ACCCAAGAAGGTCTG
CCCAAGAAGGTCTGG
CCAAGAAGGTCTGGC
CAAGAAGGTCTGGCA
AAGAAGGTCTGGCAA
AGAAGGTCTGGCAAA
GAAGGTCTGGCAAAG
AAGGTCTGGCAAAGT
AGGTCTGGCAAAGTC
GGTCTGGCAAAGTCA
GTCTGGCAAAGTCAG
TCTGGCAAAGTCAGG
CTGGCAAAGTCAGGC
TGGCAAAGTCAGGCT
GGCAAAGTCAGGCTC
GCAAAGTCAGGCTCA
CAAAGTCAGGCTCAG
AAAGTCAGGCTCAGG
AAGTCAGGCTCAGGG
AGTCAGGCTCAGGGA
GTCAGGCTCAGGGAG
TCAGGCTCAGGGAGA
CAGGCTCAGGGAGAC

AGGCTCAGGGAGACT
GGCTCAGGGAGACTC
GCTCAGGGAGACTCT
CTCAGGGAGACTCTG
TCAGGGAGACTCTGC
CAGGGAGACTCTGCC
AGGGAGACTCTGCCC
GGGAGACTCTGCCCT
GGAGACTCTGCCCTG
GAGACTCTGCCCTGC
AGACTCTGCCCTGCT
GACTCTGCCCTGCTG
ACTCTGCCCTGCTGC
CTCTGCCCTGCTGCA
TCTGCCCTGCTGCAG
CTGCCCTGCTGCAGA
TGCCCTGCTGCAGAC
GCCCTGCTGCAGACC
CCCTGCTGCAGACCT
CCTGCTGCAGACCTC
CTGCTGCAGACCTCG
TGCTGCAGACCTCGG
GCTGCAGACCTCGGT
CTGCAGACCTCGGTG
TGCAGACCTCGGTGT
GCAGACCTCGGTGTG
CAGACCTCGGTGTGG
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GACCTCGGTGTGGAC
ACCTCGGTGTGGACA
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CTCGGTGTGGACACA
TCGGTGTGGACACAC
CGGTGTGGACACACG
GGTGTGGACACACGC
GTGTGGACACACGCT
TGTGGACACACGCTG
GTGGACACACGCTGC
TGGACACACGCTGCA
GGACACACGCTGCAT
GACACACGCTGCATA
ACACACGCTGCATAG
CACACGCTGCATAGA
ACACGCTGCATAGAG

Sub A3 Cont.

CACGCTGCATAGAGC ATTCTGCCTACCTAT GGGGGAAAAGTATTT
ACGCTGCATAGAGCT TTCTGCCTACCTATT GGGGAAAAGTATTTT
CGCTGCATAGAGCTC TCTGCCTACCTATTA GGGAAAAGTATTTTT
GCTGCATAGAGCTCT CTGCCTACCTATTAG GGAAAAGTATTTTTG
TGCATAGAGCTCTC TGCCTACCTATTAGC GAAAAGTATTTTTGA
GCATAGAGCTCTCCT GCCTACCTATTAGCT AAAAGTATTTTTGAG
CATAGAGCTCTCCTT CCTACCTATTAGCTT AAAGTATTTTTGAGA
ATAGAGCTCTCCTTG CTACCTATTAGCTTT AAGTATTTTTGAGAA
TAGAGCTCTCCTTGA TACCTATTAGCTTTT AGTATTTTTGAGAAG
AGAGCTCTCCTTGAA ACCTATTAGCTTTTC GTATTTTTGAGAAGT
GAGCTCTCCTTGAAA CCTATTAGCTTTTCT TATTTTTGAGAAGTT
AGCTCTCCTTGAAAA CTATTAGCTTTTCTT ATTTTTGAGAAGTTT
GCTCTCCTTGAAAAC TATTAGCTTTTCTTT TTTTTGAGAAGTTTG
CTCTCCTTGAAAACA ATTAGCTTTTCTTTA TTTTGAGAAGTTTGT
TCTCCTTGAAAACAG TTAGCTTTTCTTTAT TTTGAGAAGTTTGTC
CTCCTTGAAAACAGA TAGCTTTTCTTTATT TTGAGAAGTTTGTCT
TCCTTGAAAACAGAG AGCTTTTCTTTATTT TGAGAAGTTTGTCTT
CCTTGAAAACAGAGG GCTTTTCTTTATTTT GAGAAGTTTGTCTTG
CTTGAAAACAGAGGG CTTTTCTTTATTTTT AGAAGTTTGTCTTGC
TTGAAAACAGAGGGG TTTTCTTTATTTTTT GAAGTTTGTCTTGCA
TGAAAACAGAGGGGT TTTCTTTATTTTTTT AAGTTTGTCTTGCAA
GAAAACAGAGGGGTC TTCTTTATTTTTTTA AGTTTGTCTTGCAAT
AAAACAGAGGGGTCT TCTTTATTTTTTTAA GTTTGTCTTGCAATG
AAACAGAGGGGTCTC CTTTATTTTTTTAAC TTTGTCTTGCAATGT
AACAGAGGGGTCTCA TTTATTTTTTTAACT TTGTCTTGCAATGTA
ACAGAGGGGTCTCAA TTATTTTTTTAACTT TGTCTTGCAATGTAT
CAGAGGGGTCTCAAG TATTTTTTTAACTTT GTCTTGCAATGTATT
AGAGGGGTCTCAAGA ATTTTTTTAACTTTT TCTTGCAATGTATTT
GAGGGGTCTCAAGAC TTTTTTTAACTTTTT CTTGCAATGTATTTA
AGGGGTCTCAAGACA TTTTTTAACTTTTTG TTGCAATGTATTTAT
GGGGTCTCAAGACAT TTTTTAACTTTTTGG TGCAATGTATTTATA
GGGTCTCAAGACATT TTTTAACTTTTTGGG GCAATGTATTTATAA
GGTCTCAAGACATTC TTTAACTTTTTGGGG CAATGTATTTATAAA
GTCTCAAGACATTCT TTAACTTTTTGGGGG AATGTATTTATAAAT
TCTCAAGACATTCTG TAACTTTTTGGGGGG ATGTATTTATAAATA
CTCAAGACATTCTGC AACTTTTTGGGGGGA TGTATTTATAAATAG
TCAAGACATTCTGCC ACTTTTTGGGGGGAA GTATTTATAAATAGT
CAAGACATTCTGCCT CTTTTTGGGGGGAAA TATTTATAAATAGTA
AAGACATTCTGCCTA TTTTTGGGGGGAAAA ATTTATAAATAGTAA
AGACATTCTGCCTAC TTTTGGGGGGAAAAG TTTATAAATAGTAAA
GACATTCTGCCTACC TTTGGGGGGAAAAGT TTATAAATAGTAAAT
ACATTCTGCCTACCT TTGGGGGGAAAAGTA TATAAATAGTAAATA
CATTCTGCCTACCTA TGGGGGGAAAAGTAT ATAAATAGTAAATAA
GGGGGGAAAAGTATT TAAATAGTAAATAAA

Sub A2 cont

AAATAGTAAATAAAG
AATAGTAAATAAAGT
ATAGTAAATAAAGTT
TAGTAAATAAAGTTT
AGTAAATAAAGTTTT
GTAAATAAAGTTTTT
TAAATAAAGTTTTTA
AAATAAAGTTTTTAC
AATAAAGTTTTTACC
ATAAAGTTTTTACCA
TAAAGTTTTTACCAT
AAAGTTTTTACCATT

EXAMPLE 8

Antisense oligonucleotides to IGF-I may be selected from molecules capable of interacting with one or more ~~of the following sense oligonucleotides:~~

SUB A3

TTTTTTTTTTTTTTG
TTTTTTTTTTTTTGA
TTTTTTTTTTTTGAG
TTTTTTTTTTTGAGA
TTTTTTTTTTGAGAA
TTTTTTTTTGAGAAA
TTTTTTTTGAGAAAG
TTTTTTTGAGAAAGG
TTTTTTGAGAAAGGG
TTTTTGAGAAAGGGA
TTTTGAGAAAGGGAA
TTTGAGAAAGGGAAT
TTGAGAAAGGGAATT
TGAGAAAGGGAATTT
GAGAAAGGGAATTTC
AGAAAGGGAATTTCA
GAAAGGGAATTTCAT
AAAGGGAATTTCATC
AAGGGAATTTCATCC
AGGGAATTTCATCCC
GGGAATTTCATCCCA
GGAATTTCATCCCAA
GAATTTCATCCCAAA
AATTTCATCCCAAAT

ATTTCATCCCAAATA
TTTCATCCCAAATAA
TTCATCCCAAATAAA
TCATCCCAAATAAAA
CATCCCAAATAAAAG
ATCCCAAATAAAAGG
TCCCAAATAAAAGGA
CCCAAATAAAAGGAA
CCAAATAAAAGGAAT
CAAATAAAAGGAATG
AAATAAAAGGAATGA
AATAAAAGGAATGAA
ATAAAAGGAATGAAG
TAAAAGGAATGAAGT
AAAAGGAATGAAGTC
AAAGGAATGAAGTCT
AAGGAATGAAGTCTG
AGGAATGAAGTCTGG
GGAATGAAGTCTGGC
GAATGAAGTCTGGCT
AATGAAGTCTGGCTC
ATGAAGTCTGGCTCC
TGAAGTCTGGCTCCG
GAAGTCTGGCTCCGG

AAGTCTGGCTCCGGA
AGTCTGGCTCCGGAG
GTCTGGCTCCGGAGG
TCTGGCTCCGGAGGA
CTGGCTCCGGAGGAG
TGGCTCCGGAGGAGG
GGCTCCGGAGGAGGG
GCTCCGGAGGAGGGT
CTCCGGAGGAGGGTC
TCCGGAGGAGGGTCC
CCGGAGGAGGGTCCC
CGGAGGAGGGTCCCC
GGAGGAGGGTCCCCG
GAGGAGGGTCCCCGA
AGGAGGGTCCCCGAC
GGAGGGTCCCCGACC
GAGGGTCCCCGACCT
AGGGTCCCCGACCTC
GGGTCCCCGACCTCG
GGTCCCCGACCTCGC
GTCCCCGACCTCGCT
TCCCCGACCTCGCTG
CCCCGACCTCGCTGT
CCCGACCTCGCTGTG

SUB A3 cont.

CCGACCTCGCTGTGG
CGACCTCGCTGTGGG
GACCTCGCTGTGGGG
ACCTCGCTGTGGGGG
CCTCGCTGTGGGGGC
CTCGCTGTGGGGGCT
TCGCTGTGGGGGCTC
CGCTGTGGGGGCTCC
GCTGTGGGGGCTCCT
CTGTGGGGGCTCCTG
TGTGGGGGCTCCTGT
GTGGGGGCTCCTGTT
TGGGGGCTCCTGTTT
GGGGGCTCCTGTTTC
GGGGCTCCTGTTTCT
GGGCTCCTGTTTCTC
GGCTCCTGTTTCTCT
GCTCCTGTTTCTCTC
CTCCTGTTTCTCTCC
TCCTGTTTCTCTCCG
CCTGTTTCTCTCCGC
CTGTTTCTCTCCGCC
TGTTTCTCTCCGCCG
GTTTCTCTCCGCCGC
TTTCTCTCCGCCGCG
TTCTCTCCGCCGCGC
TCTCTCCGCCGCGCT
CTCTCCGCCGCGCTC
TCTCCGCCGCGCTCT
CTCCGCCGCGCTCTC
TCCGCCGCGCTCTCG
CCGCCGCGCTCTCGC
CGCCGCGCTCTCGCT
GCCGCGCTCTCGCTC
CCGCGCTCTCGCTCT
CGCGCTCTCGCTCTG
GCGCTCTCGCTCTGG
CGCTCTCGCTCTGGC
GCTCTCGCTCTGGCC
CTCTCGCTCTGGCCG
TCTCGCTCTGGCCGA
CTCGCTCTGGCCGAC
TCGCTCTGGCCGACG
CGCTCTGGCCGACGA

GCTCTGGCCGACGAG
CTCTGGCCGACGAGT
TCTGGCCGACGAGTG
CTGGCCGACGAGTGG
TGGCCGACGAGTGGA
GGCCGACGAGTGGAG
GCCGACGAGTGGAGA
CCGACGAGTGGAGAA
CGACGAGTGGAGAAA
GACGAGTGGAGAAAT
ACGAGTGGAGAAATC
CGAGTGGAGAAATCT
GAGTGGAGAAATCTG
AGTGGAGAAATCTGC
GTGGAGAAATCTGCG
TGGAGAAATCTGCGG
GGAGAAATCTGCGGG
GAGAAATCTGCGGGC
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TCTGCGGGCCAGGCA
CTGCGGGCCAGGCAT
TGCGGGCCAGGCATC
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CGGGCCAGGCATCGA
GGGCCAGGCATCGAC
GGCCAGGCATCGACA
GCCAGGCATCGACAT
CCAGGCATCGACATC
CAGGCATCGACATCC
AGGCATCGACATCCG
GGCATCGACATCCGC
GCATCGACATCCGCA
CATCGACATCCGCAA
ATCGACATCCGCAAC
TCGACATCCGCAACG
CGACATCCGCAACGA
GACATCCGCAACGAC
ACATCCGCAACGACT
CATCCGCAACGACTA
ATCCGCAACGACTAT

TCCGCAACGACTATC
CCGCAACGACTATCA
CGCAACGACTATCAG
GCAACGACTATCAGC
CAACGACTATCAGCA
AACGACTATCAGCAG
ACGACTATCAGCAGC
CGACTATCAGCAGCT
GACTATCAGCAGCTG
ACTATCAGCAGCTGA
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TATCAGCAGCTGAAG
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TCAGCAGCTGAAGCG
CAGCAGCTGAAGCGC
AGCAGCTGAAGCGCC
GCAGCTGAAGCGCCT
CAGCTGAAGCGCCTG
AGCTGAAGCGCCTGG
GCTGAAGCGCCTGGA
CTGAAGCGCCTGGAG
TGAAGCGCCTGGAGA
GAAGCGCCTGGAGAA
AAGCGCCTGGAGAAC
AGCGCCTGGAGAACT
GCGCCTGGAGAACTG
CGCCTGGAGAACTGC
GCCTGGAGAACTGCA
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CTGGAGAACTGCACG
TGGAGAACTGCACGG
GGAGAACTGCACGGT
GAGAACTGCACGGTG
AGAACTGCACGGTGA
GAACTGCACGGTGAT
AACTGCACGGTGATC
ACTGCACGGTGATCG
CTGCACGGTGATCGA
TGCACGGTGATCGAG
GCACGGTGATCGAGG
CACGGTGATCGAGGG
ACGGTGATCGAGGGC
CGGTGATCGAGGGCT
GGTGATCGAGGGCTA

SUB A3 cont

	GTGATCGAGGGCTAC	GGACTACCGCAGCTA	AGTACTTGCTGCTGT
	TGATCGAGGGCTACC	GACTACCGCAGCTAC	GTACTTGCTGCTGTT
	GATCGAGGGCTACCT	ACTACCGCAGCTACC	TACTTGCTGCTGTTC
	ATCGAGGGCTACCTC	CTACCGCAGCTACCG	ACTTGCTGCTGTTCC
5	TCGAGGGCTACCTCC	TACCGCAGCTACCGC	CTTGCTGCTGTTCCG
	CGAGGGCTACCTCCA	ACCGCAGCTACCGCT	TTGCTGCTGTTCCGA
	GAGGGCTACCTCCAC	CCGCAGCTACCGCTT	TGCTGCTGTTCCGAG
	AGGGCTACCTCCACA	CGCAGCTACCGCTTC	GCTGCTGTTCCGAGT
	GGGCTACCTCCACAT	GCAGCTACCGCTTCC	CTGCTGTTCCGAGTG
10	GGCTACCTCCACATC	CAGCTACCGCTTCCC	TGCTGTTCCGAGTGG
	GCTACCTCCACATCC	AGCTACCGCTTCCCC	GCTGTTCCGAGTGGC
	CTACCTCCACATCCT	GCTACCGCTTCCCCA	CTGTTCCGAGTGGCT
	TACCTCCACATCCTG	CTACCGCTTCCCCAA	TGTTCCGAGTGGCTG
	ACCTCCACATCCTGC	TACCGCTTCCCCAAG	GTTCCGAGTGGCTGG
15	CCTCCACATCCTGCT	ACCGCTTCCCCAAGC	TTCCGAGTGGCTGGC
	CTCCACATCCTGCTC	CCGCTTCCCCAAGCT	TCCGAGTGGCTGGCC
	TCCACATCCTGCTCA	CGCTTCCCCAAGCTC	CCGAGTGGCTGGCCT
	CCACATCCTGCTCAT	GCTTCCCCAAGCTCA	CGAGTGGCTGGCCTC
	CACATCCTGCTCATC	CTTCCCCAAGCTCAC	GAGTGGCTGGCCTCG
20	ACATCCTGCTCATCT	TTCCCCAAGCTCACG	AGTGGCTGGCCTCGA
	CATCCTGCTCATCTC	TCCCCAAGCTCACGG	GTGGCTGGCCTCGAG
	ATCCTGCTCATCTCC	CCCCAAGCTCACGGT	TGGCTGGCCTCGAGA
	TCCTGCTCATCTCCA	CCCAAGCTCACGGTC	GGCTGGCCTCGAGAG
	CCTGCTCATCTCCAA	CCAAGCTCACGGTCA	GCTGGCCTCGAGAGC
25	CTGCTCATCTCCAAG	CAAGCTCACGGTCAT	CTGGCCTCGAGAGCC
	TGCTCATCTCCAAGG	AAGCTCACGGTCATT	TGGCCTCGAGAGCCT
	GCTCATCTCCAAGGC	AGCTCACGGTCATTA	GGCCTCGAGAGCCTC
	CTCATCTCCAAGGCC	GCTCACGGTCATTAC	GCCTCGAGAGCCTCG
	TCATCTCCAAGGCCG	CTCACGGTCATTACC	CCTCGAGAGCCTCGG
30	CATCTCCAAGGCCGA	TCACGGTCATTACCG	CTCGAGAGCCTCGGA
	ATCTCCAAGGCCGAG	CACGGTCATTACCGA	TCGAGAGCCTCGGAG
	TCTCCAAGGCCGAGG	ACGGTCATTACCGAG	CGAGAGCCTCGGAGA
	CTCCAAGGCCGAGGA	CGGTCATTACCGAGT	GAGAGCCTCGGAGAC
	TCCAAGGCCGAGGAC	GGTCATTACCGAGTA	AGAGCCTCGGAGACC
35	CCAAGGCCGAGGACT	GTCATTACCGAGTAC	GAGCCTCGGAGACCT
	CAAGGCCGAGGACTA	TCATTACCGAGTACT	AGCCTCGGAGACCTC
	AAGGCCGAGGACTAC	CATTACCGAGTACTT	GCCTCGGAGACCTCT
	AGGCCGAGGACTACC	ATTACCGAGTACTTG	CCTCGGAGACCTCTT
	GGCCGAGGACTACCG	TTACCGAGTACTTGC	CTCGGAGACCTCTTC
40	GCCGAGGACTACCGC	TACCGAGTACTTGCT	TCGGAGACCTCTTCC
	CCGAGGACTACCGCA	ACCGAGTACTTGCTG	CGGAGACCTCTTCCC
	CGAGGACTACCGCAG	CCGAGTACTTGCTGC	GGAGACCTCTTCCCC
	GAGGACTACCGCAGC	CGAGTACTTGCTGCT	GAGACCTCTTCCCCA
	AGGACTACCGCAGCT	GAGTACTTGCTGCTG	AGACCTCTTCCCCAA

SUB A3 cmT.

GACCTCTTCCCCAAC
ACCTCTTCCCCAACC
CCTCTTCCCCAACCT
CTCTTCCCCAACCTC
TCTTCCCCAACCTCA
CTTCCCCAACCTCAC
TTCCCCAACCTCACG
TCCCCAACCTCACGG
CCCCAACCTCACGGT
CCCAACCTCACGGTC
CCAACCTCACGGTCA
CAACCTCACGGTCAT
AACCTCACGGTCATC
ACCTCACGGTCATCC
CCTCACGGTCATCCG
CTCACGGTCATCCGC
TCACGGTCATCCGCG
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ACGGTCATCCGCGGC
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GTCATCCGCGGCTGG
TCATCCGCGGCTGGA
CATCCGCGGCTGGAA
ATCCGCGGCTGGAAA
TCCGCGGCTGGAAAC
CCGCGGCTGGAAACT
CGCGGCTGGAAACTC
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CGGCTGGAAACTCTT
GGCTGGAAACTCTTC
GCTGGAAACTCTTCT
CTGGAAACTCTTCTA
TGGAAACTCTTCTAC
GGAAACTCTTCTACA
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AAACTCTTCTACAAC
AACTCTTCTACAACT
ACTCTTCTACAACTA
CTCTTCTACAACTAC
TCTTCTACAACTACG
CTTCTACAACTACGC
TTCTACAACTACGCC
TCTACAACTACGCCC

CTACAACTACGCCCT
TACAACTACGCCCTG
ACAACTACGCCCTGG
CAACTACGCCCTGGT
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ACTACGCCCTGGTCA
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TTACTCGGGGGGCCA
TACTCGGGGGGCCAT
ACTCGGGGGGCCATC
CTCGGGGGGCCATCA
TCGGGGGGCCATCAG
CGGGGGGCCATCAGG
GGGGGGCCATCAGGA
GGGGGCCATCAGGAT
GGGGCCATCAGGATT
GGGCCATCAGGATTG
GGCCATCAGGATTGA
GCCATCAGGATTGAG
CCATCAGGATTGAGA
CATCAGGATTGAGAA
ATCAGGATTGAGAAA
TCAGGATTGAGAAAA
CAGGATTGAGAAAAA

SUB A3 cont

	AGCATTGAGAAAAAT	CTGGTCCCTGATCCT	GGAATAAGCCCCCAA
	GGATTGAGAAAAATG	TGGTCCCTGATCCTG	GAATAAGCCCCCAAA
	GATTGAGAAAAATGC	GGTCCCTGATCCTGG	AATAAGCCCCCAAAG
	ATTGAGAAAAATGCT	GTCCCTGATCCTGGA	ATAAGCCCCCAAAGG
5	TTGAGAAAAATGCTG	TCCCTGATCCTGGAT	TAAGCCCCCAAAGGA
	TGAGAAAAATGCTGA	CCCTGATCCTGGATG	AAGCCCCCAAAGGAA
	GAGAAAAATGCTGAC	CCTGATCCTGGATGC	AGCCCCCAAAGGAAT
	AGAAAAATGCTGACC	CTGATCCTGGATGCG	GCCCCCAAAGGAATG
	GAAAAATGCTGACCT	TGATCCTGGATGCGG	CCCCCAAAGGAATGT
10	AAAAATGCTGACCTC	GATCCTGGATGCGGT	CCCCAAAGGAATGTG
	AAAATGCTGACCTCT	ATCCTGGATGCGGTG	CCCAAAGGAATGTGG
	AAATGCTGACCTCTG	TCCTGGATGCGGTGT	CCAAAGGAATGTGGG
	AATGCTGACCTCTGT	CCTGGATGCGGTGTC	CAAAGGAATGTGGGG
	ATGCTGACCTCTGTT	CTGGATGCGGTGTCC	AAAGGAATGTGGGGA
15	TGCTGACCTCTGTTA	TGGATGCGGTGTCCA	AAGGAATGTGGGGAC
	GCTGACCTCTGTTAC	GGATGCGGTGTCCAA	AGGAATGTGGGGACC
	CTGACCTCTGTTACC	GATGCGGTGTCCAAT	GGAATGTGGGGACCT
	TGACCTCTGTTACCT	ATGCGGTGTCCAATA	GAATGTGGGGACCTG
	GACCTCTGTTACCTC	TGCGGTGTCCAATAA	AATGTGGGGACCTGT
20	ACCTCTGTTACCTCT	GCGGTGTCCAATAAC	ATGTGGGGACCTGTG
	CCTCTGTTACCTCTC	CGGTGTCCAATAACT	TGTGGGGACCTGTGT
	CTCTGTTACCTCTCC	GGTGTCCAATAACTA	GTGGGGACCTGTGTC
	TCTGTTACCTCTCCA	GTGTCCAATAACTAC	TGGGGACCTGTGTCC
	CTGTTACCTCTCCAC	TGTCCAATAACTACA	GGGGACCTGTGTCCA
25	TGTTACCTCTCCACT	GTCCAATAACTACAT	GGGACCTGTGTCCAG
	GTTACCTCTCCACTG	TCCAATAACTACATT	GGACCTGTGTCCAGG
	TTACCTCTCCACTGT	CCAATAACTACATTG	GACCTGTGTCCAGGG
	TACCTCTCCACTGTG	CAATAACTACATTGT	ACCTGTGTCCAGGGA
	ACCTCTCCACTGTGG	AATAACTACATTGTG	CCTGTGTCCAGGGAC
30	CCTCTCCACTGTGGA	ATAACTACATTGTGG	CTGTGTCCAGGGACC
	CTCTCCACTGTGGAC	TAACTACATTGTGGG	TGTGTCCAGGGACCA
	TCTCCACTGTGGACT	AACTACATTGTGGGG	GTGTCCAGGGACCAT
	CTCCACTGTGGACTG	ACTACATTGTGGGGA	TGTCCAGGGACCATG
	TCCACTGTGGACTGG	CTACATTGTGGGGAA	GTCCAGGGACCATGG
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SUB A3 cont

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SUB A3 cont.

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SuB A3 cont

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SUB A3 Cont

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SUBA3 cont

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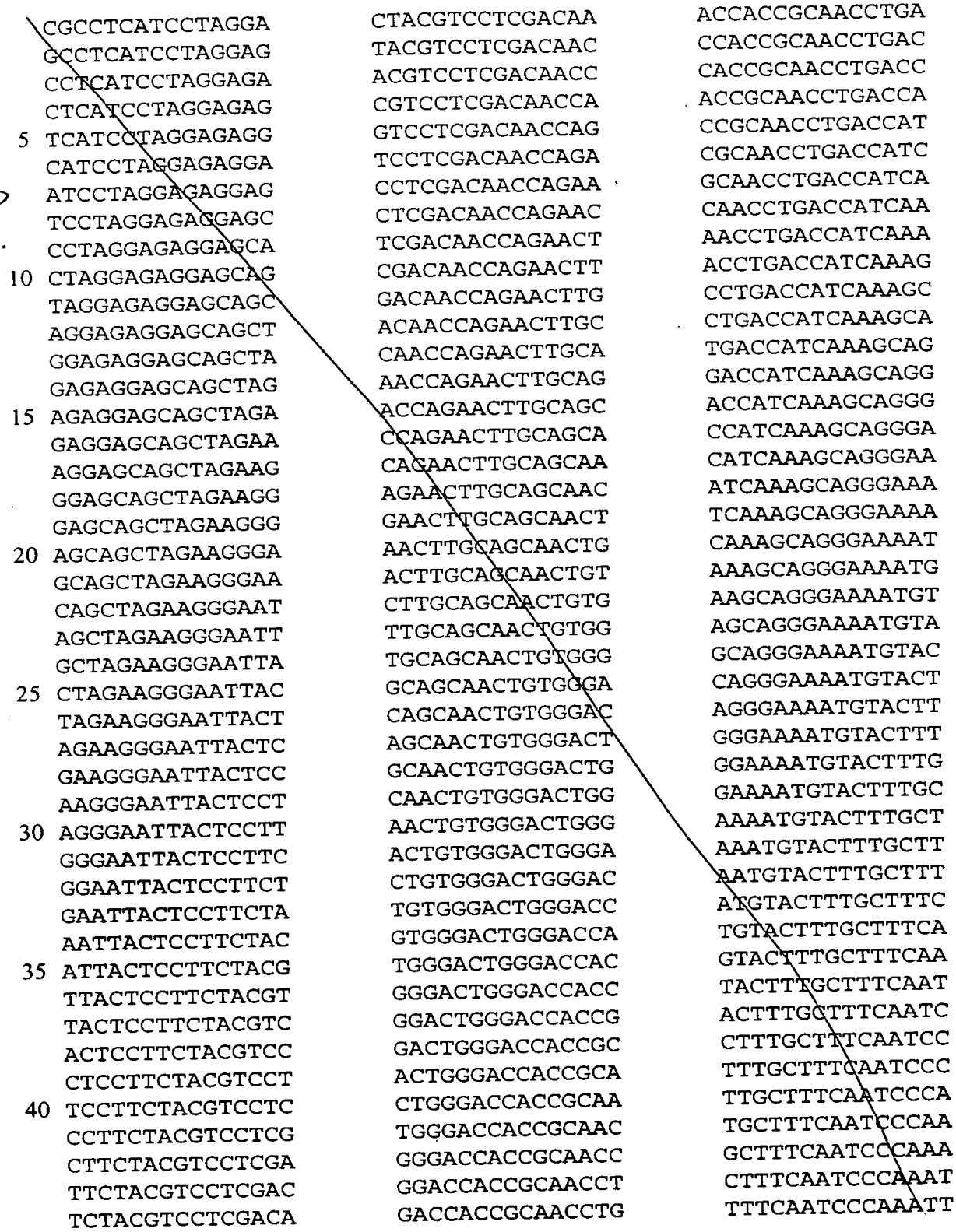

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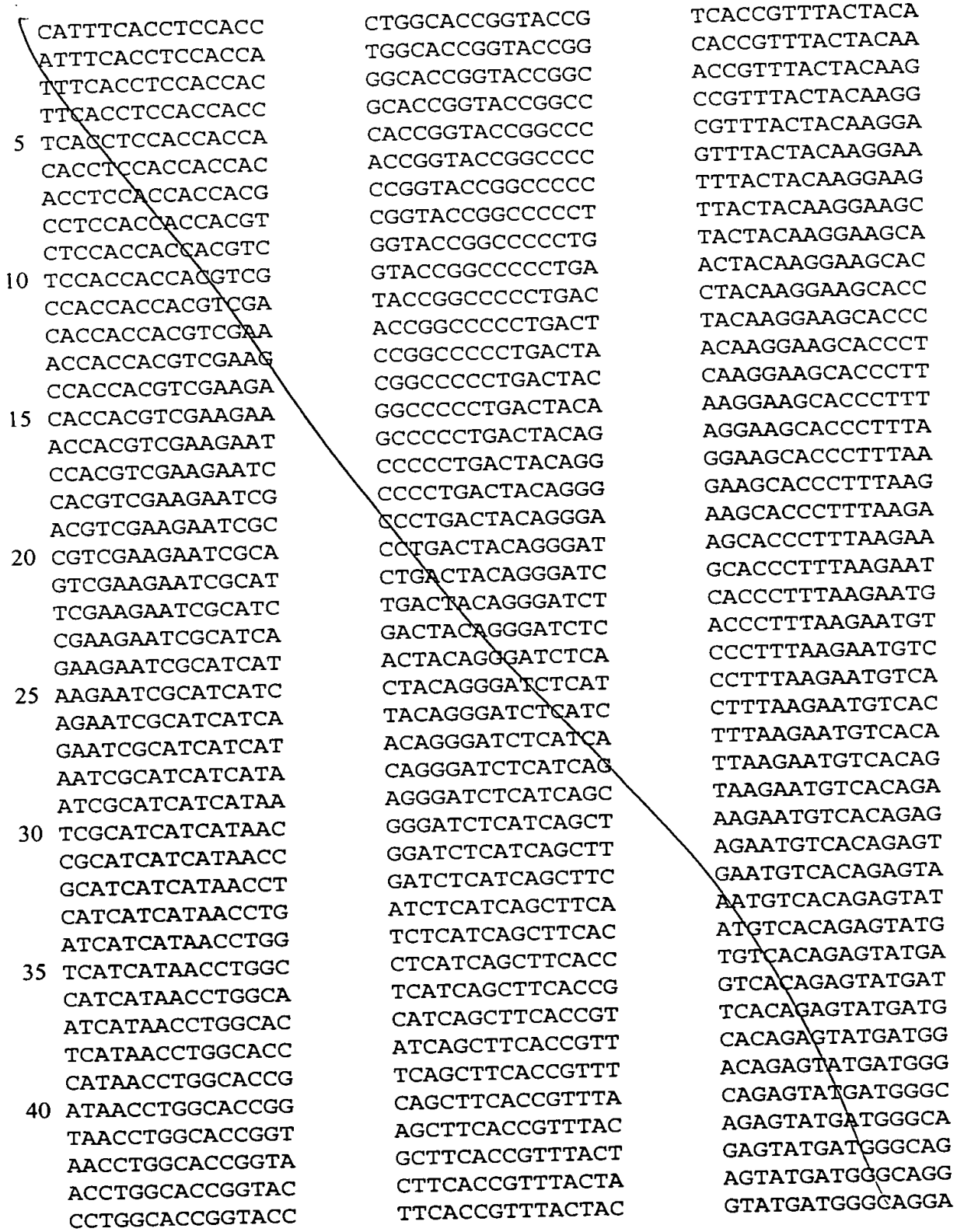

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Sub A3 Cont

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SUB A3 cont

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SUB A3 CONT.

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SUB A3 cont

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SUB A3 cont.

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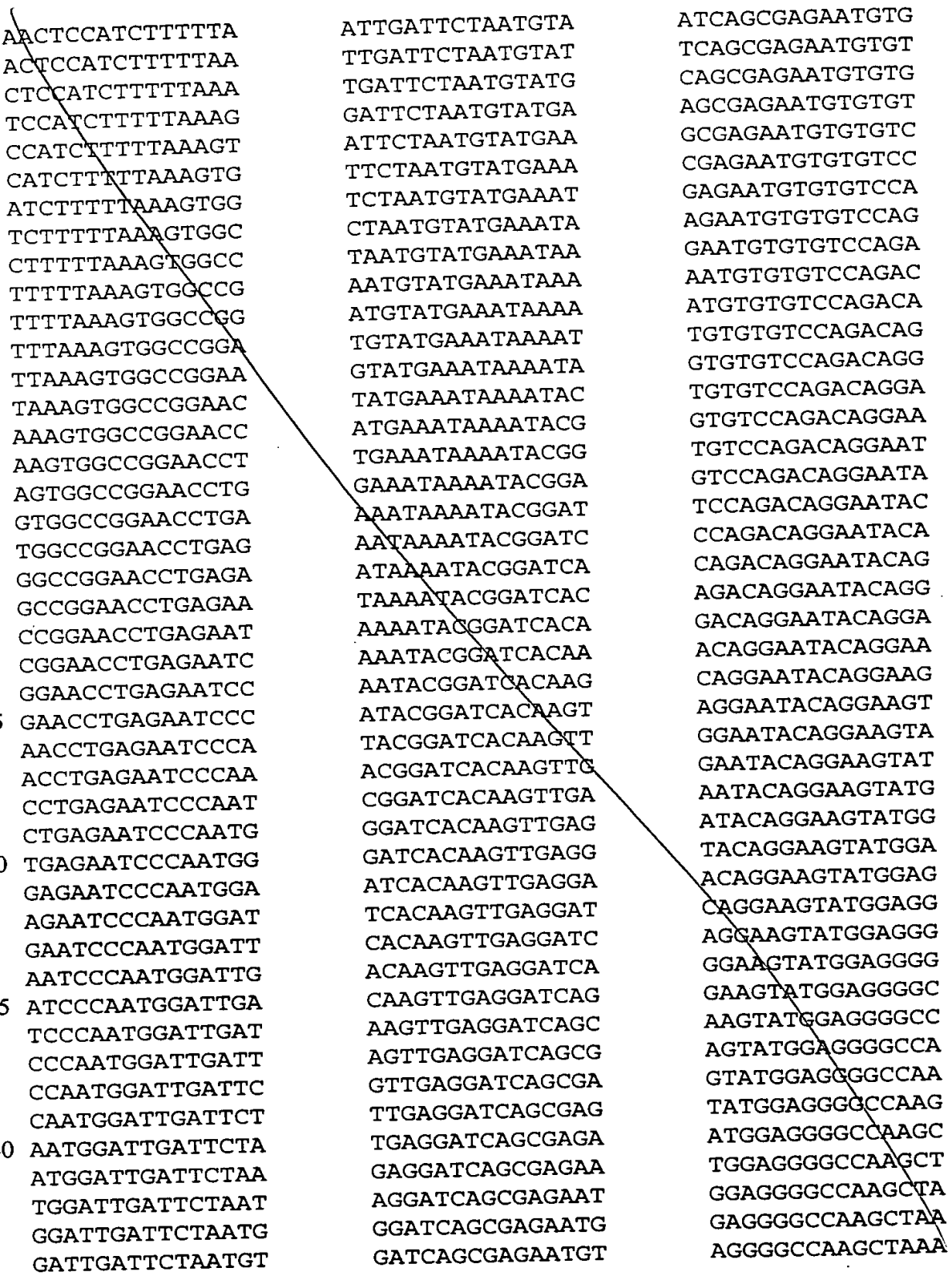
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SUB A3 cont.

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SUB A3 cont.

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SUB A3 cont

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SUBA3 Cont

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SUB A2 Cont

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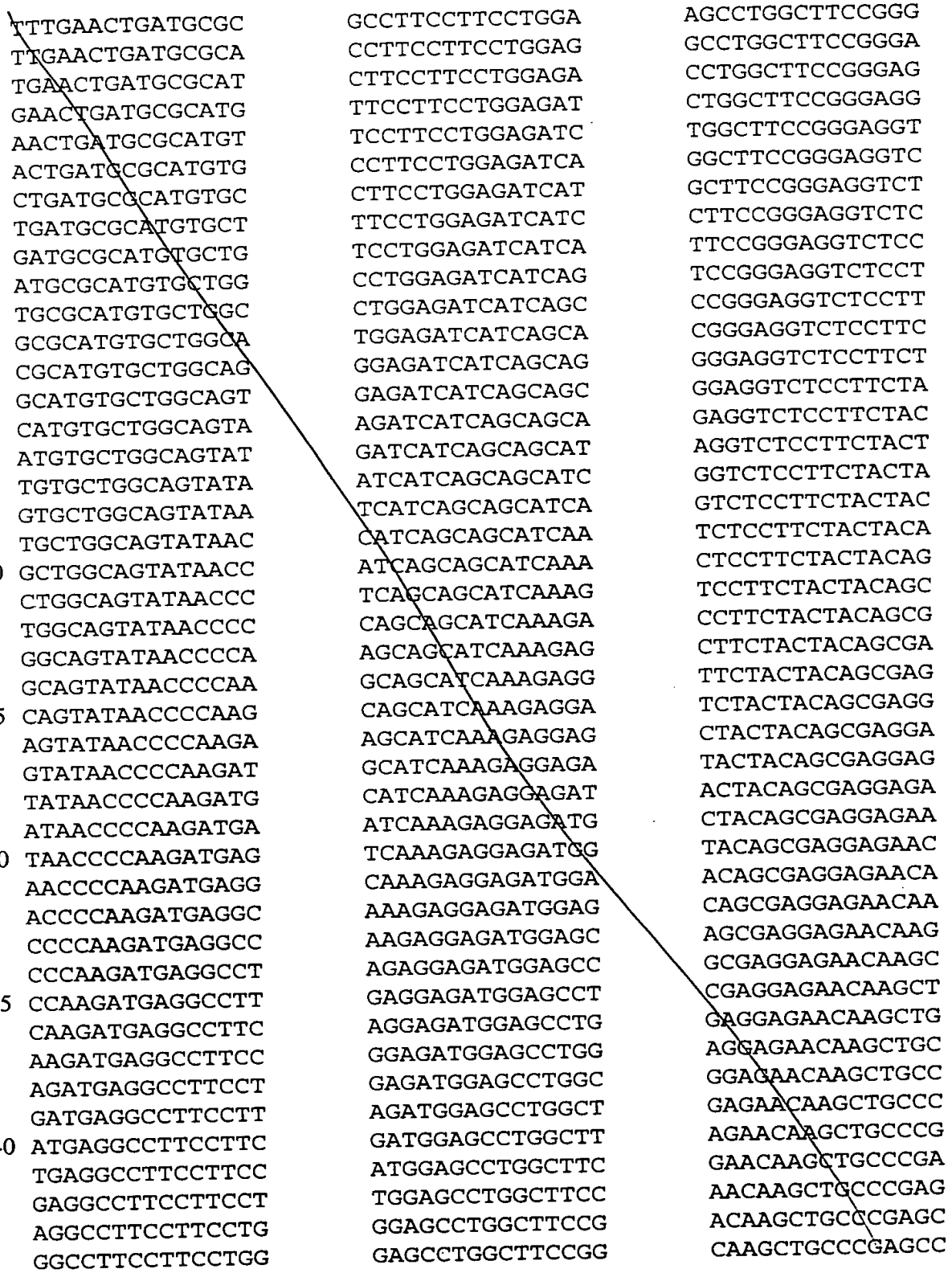

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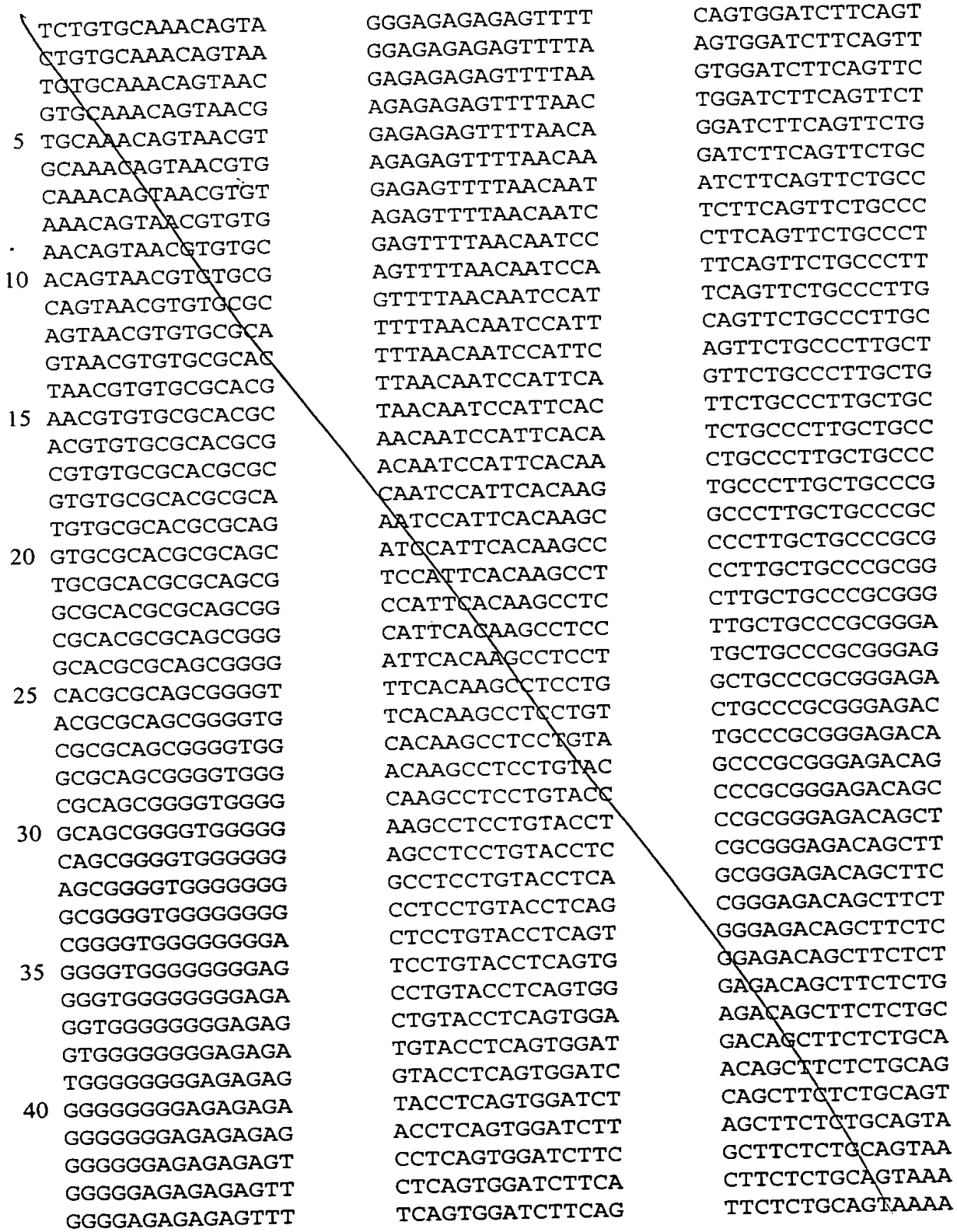
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	GTTCTCCCTTTCTCT	TTGCCACAAGTCCAG	AGTGGCTGTCCCTGT
40	TTCTCCCTTTCTCTC	TGCCACAAGTCCAGC	GTGGCTGTCCCTGTG
	TCTCCCTTTCTCTCT	GCCACAAGTCCAGCT	TGGCTGTCCCTGTGG
	CTCCCTTTCTCTCTC	CCACAAGTCCAGCTG	GGCTGTCCCTGTGGC
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SUB A3 cont.

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ATCCAACCACTGTAC
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CAACCACTGTACACA
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CTGTACACACCCGCC
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but A3 cont

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SUB A3 CONT

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	GAGAGACACGCTGGC	CTGTGCTGCTCAAGG	ACTAGATTATTATTT
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	GAGACACGCTGGCGA	GTGCTGCTCAAGGCC	TAGATTATTATTTGG
	AGACACGCTGGCGAC	TGCTGCTCAAGGCCA	AGATTATTATTTGGG
	GACACGCTGGCGACA	GCTGCTCAAGGCCAC	GATTATTATTTGGGG
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	CTGCCCCTGCTGTGC	TTGCTTCTGACTAGA	GTCTTTCTCTCAGTG
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	CCCCTGCTGTGCTGC	CTTCTGACTAGATTA	TTTCTCTCAGTGAAG
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SUB A3 CONT

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AGAAGCTGAACCGGC

EXAMPLE 9

Sub-confluent HaCaT cells were treated as described above with phosphorothioate oligonucleotides IGFR.AS (antisense: 5'-ATCTCTCCGCTTCCTTTC-3'; (SEQ ID NO. 10) ~~(<400>10)~~; (SEQ ID NO. 11) ref 13) and IGFR.S (sense control: 5'-GAAAGGAAGCGGAGAGAT-3'; ~~(<400>11)~~; ref 13) IGF-I binding to the cell monolayers was then measured as ^{125}I-IGF-I.

EXAMPLE 10

The results of this experiment are shown in Figures 7 and 8.

HaCaT cells were initially plated in DMEM with 10% v/v serum, then AS oligo experiments were performed in complete "Keratinocyte-SFM" (Gibco) to exclude the influence of exogenous IGFBPs. Oligos were synthesised as phosphorothioate (nuclease-resistant) derivatives (Bresatec, South Australia) and were as follows: antisense: AS2, 5'-GCGCCCGCTGCATGACGCCTGCAAC-3' (SEQ ID NO. 4) (IGFBP-3 start codon); controls: AS2NS, 5'-CGGAGATGCCGCATGCCAGCGCAGG-3' (SEQ ID NO. 5); AS4,

5'-AGGCGGCTGACGGCACTA-3' (SEQ ID NO. 6); AS4NS, 5'-GACAGCGTCGGAGCGATC-3' (SEQ ID NO. 9); IGFRAS, 5'-ATCTCTCCGCTTCCTTTC-3' (SEQ ID NO. 10); IGFRS, 5'-GAAAGGAAGCGGAGAGAT-3' (SEQ ID NO. 11). Oligos to IGFBP-3 were based on the published sequence of Spratt *et al* [12]. AS oligos were added to HaCaT monolayers in 0.5ml medium in 24-well plates at the concentrations and addition frequencies indicated. IGFBP-3 measured in cell-conditioned medium using a dot-blot assay, adapted from the Western ligand blot method of Hossenlopp *et al* [11], in which 100μl of conditioned medium was applied to nitrocellulose filters with a vacuum dot-blot apparatus. After drying the membranes at 37°C, relative amounts of IGFBP are determined by ^{125}I-IGF-I-binding, autoradiography and computerised imaging densitometry. Triplicate wells (except in Figure 7, where duplicate wells were measured as shown) were analysed and corrected for changes in cell number per well. Relative cell number per well was determined using an amido black dye method, developed specifically for cultured monolayers of HaCaT cells [14]. Cell numbers differed by less than 10% after treatment. For oligos to the IGF receptor, receptor quantitation in intact HaCaT monolayers was by overnight incubation with ^{125}I-IGF-I (30,000cpm/well) at 4°C.

EXAMPLE 11

Experiments involving ribozymes are generally conducted as described in International Patent Application No. WO 89/05852 and in Haselhoff and Gerlach [8]. Ribozymes are constructed with a hybridising region which is complementary in nucleotide sequence to at least part of a target RNA which, in this case, encodes IGFBP-2. Activity of ribozymes is measurable on, for example, Northern blots or using animal models such as in the nude mouse model (15; 16) or the "flaky skin" mouse model (17; 18).

EXAMPLE 12

The methods described in Example 11 are used for the screening of ribozymes which inhibit IGFBP-3 production. The activity of the ribozymes is determined as in Example 11.

EXAMPLE 13

The methods described in Example 11 are used for the screening of ribozymes which inhibit IGF-1 production. The activity of the ribozymes is determined as in Example 11.

EXAMPLE 14

The methods described in Example 11 are used for the screening of ribozymes which inhibit IGF-1 production. The activity of the ribozymes is determined as in Example 11.

EXAMPLE 15

Twenty-one antisense oligonucleotides targeted to mRNA sequences enducing the IGF-1 receptor, and four random oligonucleotides were synthesized. The antisense oligonucleotides are C5-propynyl-dU, dC 15mer phosphorothioate oligodeoxyribonucleotides. In these oligonucleotides, a phosphorothioate backbone replaces the phosphodiester backbone of naturally occurring DNA. The positions of the 21 sequence specific antisense oligonucleotides relative to the IGF-1 receptor mRNA structure are shown in Figure 9.

EXAMPLE 16

Experiments were performed to determine the uptake of the antisense oligonucleotides of Example 15 into keratinocytes. Cells of the differentiated human keratinocyte cell line, HaCaT, were incubated for 24 hours in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% (w/v) fetal calf serum (FCS) containing fluorescently labelled oligonucleotide (R451, a randomized sequence oligonucleotide, 30nM) and cytofectin GSV (2μg/ml, Glen Research, 44901 Falcon Place, Sterling, VA 20166, Cat. No. 70-3815-78). Cells were then transferred to oligonucleotide-free medium and fluorescence microcopy and phase contrast images of the cells were obtained. Figure 10 shows fluorescence microscopy (Panel A) and phase contrast (Panel B) images of uptake of fluorescently labelled oligonucleotide in the majority of cells in a HaCaT monolayer. The degree of uptake obtained with the cationic lipid cytofectin was far greater than the uptake obtained with the next best lipid tried, Tfx-50.

A further experiment was performed to assess the uptake and toxicity associated with the use of cytofectin GSV over five days. Confluent HaCaT keratinocytes were incubated in DMEM containing fluorescently labelled oligonucleotide R451 (30nM or 100 nM) plus cytofectin GSV (2μg/ml or 5μg/ml) over 120 hours, viewed by fluorescence microscopy, tryptan blue stained, and counted. The graphs in Figure 11 depict uptake (Panel A) and toxicity (Panel B). The proportion of cells containing oligonucleotide remained high over the 120 hour period. The combination of 30 nM oligonucleotide and 2μg/ml GSV provided optimal uptake and minimal toxicity.

EXAMPLE 17

The twenty-one oligonucleotides of Example 15 were then screened for their ability to inhibit IGF-I receptor mRNA levels in HaCaT cells, in accordance with the teachings herein. HaCaT cells were grown to 90% confluence in DMEM supplemented with 10% (v/v) FCS. Antisense oligonucleotides (30nM) were completed with cytofectin GSV (2μg/ml) and added to the cells in the presence of serum. HaCaT keratinocytes were treated with the oligonucleotide/GSV complexes or randomized sequence oligonucleotides (R451, R766), liposome alone (GSV), or were left untreated (UT). Duplicate treatments were performed. Repeat additions of the oligonucleotides/GSV complex were performed at 24, 48 and 76 hours following the first addition. Total RNA was isolated as per the RNAzolB protocol (Biotecx Laboratories, Inc. 6023 South Loop East, Houston, TX 77033) 96 hours following the first addition.

IGF-I receptor mRNA and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA levels were simultaneously determined by a ribonuclease (RNase) protection assay. The RNase Protection Assay kit, *in vitro* transcription kit, and IGF-I receptor and GAPDH DNA templates were obtained from Ambion, Inc. (2130 Woodward St., Houston, TX 78744). The amount of IGF-I receptor mRNA in any given sample was expressed as the amount of IGF-I receptor mRNA relative to the amount of GAPDH mRNA. Each oligonucleotide was tested in at least two separate experiments.

Figure 12 depicts representative results of the screening process. Panel A shows an electrophoretic analysis of IGF-I receptor and GAPDH mRNA fragments after RNase protection. Molecular weight markers are shown on the right hand side. The full-length probe is shown on the left hand side; G-probe indicates the IGF-I receptor probe. GAPDH protected fragments (G) are seen at 316 bases and IGF-I protected fragments (I) are seen at 276 bases. Exhibit E, Panel B provides a graph indicating the relative level of IGF-I receptor mRNA following each treatment.

The results obtaining from the above screening assays are summarized in Figure 13. The graph depicts the relative level of IGF-I receptor mRNA after treatment with oligonucleotides complementary to the human IGF-I receptor mRNA (26-86), four randomized sequence oligonucleotides (R1, R4, R7, R9), liposome alone (GSV), or no treatment (UT). Asterisks indicate a significant different in relative IGF-I receptor mRNA as compared to GSV treated cells ($n=4\text{-}10$, $p<0.05$).

As demonstrated in Figure 13, treatment with eighteen of the twenty-one oligonucleotides resulted in a significant different in levels of IGF-I receptor mRNA relative to GSV treated cells. Three of the antisense oligonucleotides tested in the screening assay reduce IGF-I receptor mRNA to less than 35% of GSV-treated cells. These antisense oligonucleotides have the following sequences, presented in the 5′ to 3′ direction:

#27 UCCGGAGCCAGACUU^ (SEQ ID NO. 12)
#64 CACAGUUGCUGCAAG^ (SEQ ID NO. 13)
#78 UCUCCGCUUCCUUUC^ (SEQ ID NO. 14)

As further demonstrated in Figure 13, six of the antisense oligonucleotides tested in the screening assay reduce IGF-I receptor mRNA to between 35 and 50% of GSV-treated cells. These antisense oligonucleotides have the following sequences, presented in the 5′ to 3′ direction:

#28 AGCCCCCACAGCGAG^ (SEQ ID NO. 15)
#32 GCCUUGGAGAUGAGC^ (SEQ ID NO. 16)
#40 UAACAGAGGUCAGCA^ (SEQ ID NO. 17)
#42 GGAUCAGGGACCAGU^ (SEQ ID NO. 18)
#46 CGGCAAGCUACACAG^ (SEQ ID NO. 19)
#50 GGCAGGCAGGCACAC^ (SEQ ID NO. 20)

EXAMPLE 19

Another experiment was performed demonstrating that antisense oligonucleotides targeted to genetic sequences encoding the IGF0I receptor and that reduce IGF-I receptor mRNA levels also inhibit the IGF-I receptor level on the surface of the treated cultured keratinocytes. HaCaT cells were grown to confluence in 24-well plates in DMEM containing 10% (v/v) FCS. Oligodeoxynucleotide and cytofectin GSV were mixed together in serum-free DMEM, and incubated at room temperature for 10 minutes before being diluted ten-fold in medium and placed on the cells. Cells were incubated for 72 hours with 30nM random sequence or antisense oligonucleotide and 2μm/ml GSV, or with GSV alone in DMEM containing 10% (v/v) FCS with solutions replaced every 24 hours. This was followed by incubation with oligonucleotide/GSV in serum-free DMEM for 48 hours. All incubations were performed at 37°C. Cells were washed twice with 1ml cold PBS. Serum-free DMEM containing 10^{-10}M ^{125}I-IGF-I was added with or without the IGF-I analogue, des (1-3) IGF-I, at 10^{-11}M to 10^{-7}M. Cells were incubated at 4°C for 17 hours with gentle shaking, then washed three times with 1ml cold PBS and lysed in 250μl 0.5M NaOH/0.1% (v/v) Triton X-100 at room temperature for 4 hours. Specific binding of the solubilised cell extract was measured using a gamma counter. As shown in Figure 14, treatment of HaCaT keratinocytes with oligonucleotide reduced cell surface IGF-I receptor levels to 30% of levels in untreated keratinocytes or in keratinocytes treated with liposome alone or a random oligonucleotide, R766. As shown in Figure 15, treatment with oligonucleotide #27 also significantly reduced cell surface IGF-I receptor levels relative to untreated keratinocytes or treatment with liposome alone or random nucleotide R451. As demonstrated in Example 17,

oligonucleotides #64 and #27 reduce IGF-I receptor mRNA levels in cultured keratinocytes to less than 35% of GSV-treated cells. Accordingly, the ability of an oligonucleotide to reduce IGF-I receptor mRNA levels in correlated with its ability to reduce cell surface IGF-I receptor levels.

The forgoing Examples demonstrate that antisense oligonucleotides targeted to the IGF-I receptor can be delivered to human keratinocytes *in vitro*, can inhibit IGF-I receptor mRNA levels in human keratinocytes *in vitro*, and that inhibition of mRNA levels is correlated with reduction of cell surface IGF-I receptor levels.

EXAMPLE 19

Further experiments demonstrated the efficacy of antisense oligonucleotides targeted tot he IGF-I receptor in an *in vivo* model of psoriasis. An animal model of psoriasis is the human psoriatic skin xenograft model. The skin used in this model contains the true disease state. In this model, reduction in epidermal thickness of psoriatic grafts in response to treatment is positively correlated with efficacy of treatment. Both normal and psoriatic human skin were ~~grated~~ grafted into ~~a thymic (nude) mice in accordance with~~ a thymic (nude) mice in accordance with the methods of Baker *et al* (1992) *Brit. J. Dermatol.* 126:105 and Nanney *et al* (1992) *J. Invest. Dermatol,* 92:296. Successful grafting was achieved, as demonstrated in Figure 16, which shows hemotoxylin and eosin (H&E) stained sections of a 49-day old psoriatic human skin graft (Panel B) compared to the histology of the skin graft prior to grafting (Panel A). The histological features of psoriasis present in the pregraft section (e.g., parakeratosis, acanthosis and pronounced rete ridges) are present in the grafts more than seven weeks post grafting.

Using the model, oligonucleotide uptake was measured in epidermal keratinocytes *in vivo* after intradermal injection. Fluorescently labelled oligonucleotide (R451, 50μl, 10μM injection) was intradermally injected into psoriatic and normal skin grafts on a thymic mice. Live confocal microscopy and fluorescence microscopy of fixed sections was then employed.

Using both techniques, oligonucleotide was found to localize in the nucleus of over 90% of basal keratinocytes. Figure 17 shows the nuclear localization of oligonucleotide in psoriatic skin cells using conventional fluorescence microscopy of a graft that was removed and sectioned after 24 hours.

After establishing oligonucleotide uptake in the *in vivo* model, a small number of pilots experiments were performed to determine a schedule for treatment of ~~grated~~ grafted mice with antisense oligonucleotides targeted to genetic sequences encoding the IGF-I receptor. The treatment schedule was finalized as follows:

Graft Number	Treatment	Volume of Injection	ODN Concentration	Duration of Treatment
1-3	Vehicle (PBS)	50μl	-	20 days
4-6	RandomODN#R451	50μl	10μM	20 days
7-9	ODN#27	50μl	10μM	20 days
10-12	ODN#74	50μl	10μM	20 days
13-15	ODN#50	50μl	10μM	20 days

As determined above, oligonucleotide #27 (ODN #27) reduced IGF-I receptor mRNA *in vitro* to less than 35% of GSV-treated cells. Oligonucleotide #50 (ODN#50) reduced IGF-I receptor mRNA *in vitro* to between 35 and 50% of GSV-treated cells. Oligonucleotide #74 (ODN #74) was not inhibitory to IGF-I receptor mRNA *in vitro*. In the *in vivo* model, each mouse received two grafts. Random oligonucleotide or vehicle was injected intradermally in one graft and acted as a control. The second graft was injected with the targeted oligonucleotide. Each graft received an injection every second day for the duration of the treatment.

Histology of representative grafts from each treatment type are shown in Figures 18(a)-(d) and 19(a) - (d). Each sheet shows three images of H&E stained sections: the pregraft histology, the control treated graft, and the targeted oligonucleotide treated graft. Figures 18(a)-(d) are shown at 100x magnification; figures 19(a)-(d) are shown at 400x magnification. The total cross sectional area of epidermis of each graft was assessed using MCID analysis software. The pooled results from all of the treated grafts are shown in Figure 20.

As shown in Figures 18(a)-(d) and 19(a)-(d), the vehicle-treated (control) grafts were marginally thinner than thepregraft sections. The degree of regression in these

experiments (ie., less than 10%) is not significant. A similar amount of marginal thinning of epidermis compared to pregraft also occurred in pilot experiments in which psoriatic grafts were not injected, and thus it is unlikely that the vehicle itself has any effect. Histological features of psoriasis present in skin samples prior to grafting (clubbing of rete ridges, parakeratosis, acanthosis) were present in these grafts.

The random oliognucleotide treated grafts varied in epidermal thickness after 20 days of treatment. Grafts were either a similar thickness to the pregraft histology, or marginally thinner. Random oligonucleotide treated grafts were in each case significantly thicker than their targeted oligonucleotide treated pairs.

As shown in Figure 20, the targeted oligonucleotide treated grafts were significantly thinner than the pregraft sections and showed less parakeratosis and clubbing of rete ridges. Antisense oligonucleotides which were effective at reducing IGF-I receptor mRNA levels *in vitro* (#27 and #50) produced greatere epidermal thinning than an oligonucleotide which was not inhibitory to IGF-I receptor mRNA *in vitro* (#74). Accordingly, there is a direct correlation between the ability of an oligonucleotide targeted to the IGF-I receptor to inhibit IGF-I receptor mRNA levels *in vitro* and the efficacy of the oligonucleotide as an anti-psoriasis agent in an *in vivo* model.

EXAMPLE 20

Another experiment demonstrated that treatment of psoriatic grafts with an oligonucleotide targeted to a genetic sequence encoding the IGF-I receptor results in inhibition of proliferation. Pregrafts from psoriatic patients, control grafts treated with R4541, and grafts treated with oligonucleotide #27 were obtained as described in Example 19. An antibody to the cell cycle-specific nuclear antigen Ki67 was used to immunohistochemically detect actively dividing cells and thereby assess proliferation. The αKi67 antibody (DAKO, Glostrup, Denmark) recognizes the Ki67 antigen transiently expressed in nuclei of proliferating cells during late G_1, S, M and G_2 phases of the cycle

and thus provides a marker for proliferation. Pregraft and graft sections were immunohistochemically processed by standard methods using αKi67 (according to the manufacturer's instructions), peroxidase-conjugated anti-rabbit second stage antibody, and a chromogenic peroxidase substrate.

The results of this experiment are presented in Figure 21 as immunohistochemical sections at 100x magnification. The top panel of Figure 21 depicts a pregraft section obtained from a psoriatic patient. The epidermis is thicker than normal and nucleic are evident in the stratum corneum. Ki67 positive cells, appearing as brown dots, are evidence in the basal and suprabasal layers, and indicate actively proliferating cells. The control (R450-treated) graft in the bottom panel of Figure 21 also exhibits evidence of proliferation, including parakeratosis and Ki67-positive cells appearing as brown-staining nuclei. The center panel of Figure 21 exhibits the oligonucleotide #27-treated graft. This graft exhibits significantly reduced proliferation as evidenced by normal (thin) epidermis, lack of invaginations, and substantial loss of Ki67-positive cells.

These results indicate that treatment of human psoriatic grafts with an oligonucleotide targeted to mRNA encoding the IGF-I receptor results in inhibition of epidermal proliferation.

EXAMPLE 21

Topical formulations of complexes of oligonucleotides with cytofectin GSV in aqueous or methylcellulose gel formulations were prepared and assessed foruptake of the oligonucleotide by keratinocytes *in vivo*. The topical formulations contained oligonucleotides complexed with cytofectin GSV in an aqueous solution or methylcellulose carrier, as taught herein. With both aqueous and methylcellulose gel formulations, locatlization of oligonucleotide R451 to nuclei and cytoplasm of keratinocytes in normal human skin grafts on nuce mice was observed. Figure 22 shows an image from confocal microscopy demonstrating oligonucleotide locatlization in the nuclei and cytoplasm of

keratinocytes in normal human skin grafts after topical application of fluroescently labeled oligonucleotide (10μM R451) complexed with cytofectin GSV (10μg/ml). Figure 23 shows an image from confocal microscopy demonstrating that topical application of the same oligonucleotide/GSV concentrations in a 3% (w/v) methylcellulose gel produced similar uptake in the target keratinocyte population. Using an aqueous formulation of oligonucleotide/GSV complexes, penetration of oligonucleotide into the viable epidermis was observed, whereas application of formulations of oliognucleotide complexed with other cationic lipids resulted in localization of oligonucleotide in the stratum corneum.

EXAMPLE 22

Thirteen antisense oligonucleotides targeted to IGFBP-3 were synthesized. The antisense oligonucleotides are C5-propynyl-dU, Dc15 mer phosphorothioate oligodeoxyribonucleotides. Figure 24 attached hereto is a schematic diagram indicating the position of the thirteen oligonucleotides relative to the IGFBP-3 mRNA structure.

These oligonucleotides were screened for their ability to inhibit IGFBP-3 mRNA levels of HaCaT cells in accordance with the teachings herein. HaCaT cells were grown to 90% confluence in DMEM supplemented with 10% (v/v) FCS, then placed in complete keratinocyte serum free medium (KSFM, Gibco), which has a defined amount of EGF, for 24 hours. Oligonucleotides (30nM or 100nM) were complexed with GSV cytofectin (2μg/ml) and added to cells in complete KSFM to allow oligonucleotides to enter the nucleus before removal of EGF. Repeat additions were performed at three hours (in serum free DMEM, which releases the EGF inhibition of IGFBP-3 mRNA) and again after another 24 hours. HaCaT cells were also treated with randomized sequence oligonucleotides (R121, R451, R766 and R961), liposome alone (GSV) or were left untreated (UT). Total RNA was isolated as described in Example 17, 24 hours after the last treatment. Total RNA (15μg) was analyzed by Northern analysis and phosphoroimager quantitation for IGFBP-3 and GADPH mRNA. IGFBP-3 mRNA is expressed as the amount of IGFBP-3 mRNA relative to the amount of GAPDH mRNA.

Figures 25(a)-(d) provide graphs which depict results in this screening process. In these graphs, R1 and R12 refer to R121; R4, R4(0) and R45 rfer to R451; R7, R7(0) and R76 refer to R766; and R9 and R96 refer to R961. The values were standardized to GSV-treated cells, and data was pooled and statistically analyzed by ANOVA followed by Domet's test to compare each treatment to GSV-treated cells. The pooled data are presented as a bar graph in Figure 26. As demonstrated, at a concentration of 30nM, treatment of HaCaT cells with 8 of the 12 targeted oligonucleotides tested resulted in a statistically significant reduction in levels of IGFBP-3 mRNA relative to GSV-treated cells. At a concentration of 100nM, treatment with 9 fo the 13 targeted oligonucleotides tested resulted in a statistically significant reduction in levels of IGFBP-3 mRNA relative to GSV-treated cells.

These experiments demonstrate that antisense oligonucleotides targeted to genetic sequences encoding IGFBP-3 can inhibit IGFBP-3 mRNA levels in human keratinocytes *in vitro*.

EXAMPLE 23

IGF-I receptor is a potent mitotic signalling molecule for keratinocytes and the human receptor elicits separate intracellular signals that prevent apoptosis (19). It is proposed in accordance with the present invention that inactivation of IGF-I receptors in epidermal keratinocytes will achieve three important outcomes in subsequent UV treatment of lesions:

(i) Acute epidermal hyperplasia following UV has been suggested to increase the risk of keratinocyte carcinogenic transformation (22). By reducing IGF-I receptor expression in the epidermis, the incidence of epidermal hyperplasia following UV exposure is likely to be reduced leading to an overall acceleration in normalization of the lesion and reduced carcinogenic risk.

(ii) Inhibition of anti-apoptotic action of IGF-I receptor will enhance the reversal of epidermal thickening and accelerate normalization of differentiation. Topical or injected IGF-I receptor antisense as adjunctive treatment will increase apoptosis in the epidermal layer thereby enhancing the reduction in acanthosis observed in UV treatments.

(iii) Survival of keratinocytes, ie. those which evade apoptosis is likely to occur when cells have damaged DNA. Such mutations may be in the tumor suppressor region. Consequently, the use of antisense therapy will result in less frequent selection of mutated keratinocytes and therefore reduced incidence of basal cell carcinomas and squamous.

Accordingly, antisense therapy, especially against IGF-I-receptor is useful in combination with UV therapy in the treatment of epidermal hyperplasia.

EXAMPLE 24

HaCaT cells were treated with antisense oligonucleotides directed to IGF-I receptor mRNA. Levels of IGF-I receptor mRNA were then monitored. In essence, confluent HaCaT cells were treated every 24 hours for four days with 2 μg/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific oligonucleotides (#26 to #86) or random sequence oligonucleotides (*R121, R451 and R766*). Figure 27(a) is a photographic representation showing representative RNase protection assay gel showing IGF-I receptor (IGFR) and GAPDH mRNA in untreated or treated HaCaT cells. Figure 27(b) is a densitometric quantification of IGF-I receptor mRNA in a HaCaT cells following treatment with IGF-I receptor specific oligonucleotides (solid black) random sequence oligonucleotides (horizontal striped bar) or GSV alone (shaded bar) compared to untreated cells (UT, vertical striped bar).

EXAMPLE 25

In this example, reduction in total cellular IGF-I receptor protein was monitored following antisense oligonucleotide treatment. Confluence HaCaT cells were treated with 24 hours for 4 days with 2 μg/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific AONS (#27, #50 and #64) or the random sequence oligonucleotide, R451. Total cellular protein was isolated and analysed for IGF-I receptor by SDS PAGE followed by western blotting with antibody specific for the human IGF-I receptor. Figure 28(a) shows duplicate treated cellular extracts following the IGF-I receptor at the predicted size of 110 kD. Figure 28(b) is a densitometric quantification of IGF-I receptor protein.

EXAMPLE 26

The reduction in IGF-I receptor numbers was determined on the keratinocyte cell surface after antisense oligonucleotide treatment. HaCaT cells were tranfected with IGF-I receptor specific AONs #27, #50, #64, a random sequence oligonucleotides (R451) or following treatment with GSV a lipid alone every 24 hours for 4 days. Competition binding assays using ^{125}I-IGF-I and the receptor-specific analogue, des(1-3)IGF-I were performed. Results are shown in Figure 29.

EXAMPLE 27

In this example, the apoptotic protecting effects of IGF-I receptor on keratinocyte cells was tested by following the reduction in keratino cell numbers following antisense oligonucleotide treatment. HaCaT cells, initially at 40% confluence, were transfected with the IGF-I receptor specific AON #64, control sequences R451 and 6414 or treated with GSV a lipid alone every 24 hours for 2 days. The cell number was measured in culture wells using a dye binding assay. The results are presented in Figure 30. The results clearly confirm that the IGF-I receptor exhibits an anti-apoptotic effect. By reducing IGF-I receptor levels using antisense oligonucleotide treatment, the anti-apoptotic effect is interrupted and apoptosis results in the reduction in keratinocyte cell number. Results are shown in Figure 30.

EXAMPLE 28

This example shows a reversal of epidermal hyperplasia in psoriatic human skin grafts on nude mice following intradermal injection with antisense oligonucleotides. Grafted psoriasis lesions were injected with IGF-I receptor specific AONs, a random sequence oligonucleotide in PBS, or with PBS alone, every 2 days for 20 days, then analysed histologically. The results are shown in Figure 31. In Figure 31(a), donor A graft treated with AON #50 showing epidermal thinning compared with the pregraft and control (PBS) treated graft and donor graft treated with AON #27 showing epidermal thinning compared with pregraft and control (R451) treated graft. In Figure 31(b), the mean epidermal cross-sectional area over the full width of grafts is shown as determined by digital image analysis. The results show that epidermal hyperplasia is reversed following the intradermal injection of antisense oligonucleotides.

EXAMPLE 29

Figure 32 shows the reversal of epidermal hyperplasia correlating with reduced IGF-I receptor mRNA in grafted psoriasis lesions treated with antisense oligonucleotides. Figure 32(a) shows a psoriasis lesion prior to grafting and after grafting and treatment with IGF-I receptor specific oligonucleotide #27 (AON #27) or random sequence (R451) immunostained with antibodies to Ki67 to identify proliferating cells. Proliferating cells are indicated by a dark brown nucleus (arrows). Figure 32(b) shows the same lesion prior to grafting and after oligonucleotide treatment as in Figure 32(a) but subjected to *in situ* hybridisation with ^{35}S-labelled cRNA probe complementary to the human IGF-I receptor mRNA. The presence of IGF-I receptor mRNA is indicated by silver grains which are almost eliminated in the epidermis of the lesion treated with IGF-I receptor specific oligonucleotide # 27 (AON #27). This experiment shows that reversal of epidermal hyperplasia correlates with reduced IGF-I receptor mRNA in grafted psoriasis lesions treated with antisense oligonucleotides.

EXAMPLE 30

Figure 33 treatment with oligonucleotides. HaCaT cell monolayers were grown to 90% confluence in DMEM containing 10% fetal calf serum treated every 24 hours for two days with 2 μg/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Total RNA was isolated and analysed for IGF-I receptor and GAPDH mRNA using a commercially available ribonuclease protection assay kit. The results show a reduction in IGF-I receptor mRNA in the HaCaT keratinocyte cells.

EXAMPLE 31

Figure 34 treatment with oligonucleotides. HaCaT cell monolayers were grown to 90% confluence in DMEM containing 10% fetal calf serum treated every 24 hours for 4 days with 2 μg/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Cells were lysed in a buffer containing 50 mM HEPES, 150 mM NaCl, 10% v/v glycerol, 1 v/v Trison X-100 and 100 μg/ml aprotinin on ice for 30 minutes, then 30 μg of lysate was loaded onto a denaturing 7% w/v polyacrylamide gel followed by transfer onto an Immobilon-P membrane. Membranes were then incubated with anti-IGF-I receptor antibodies C20 (available from Santa Cruz Biotechnology Inc., Santa Cruz, California) for 1 hour at room temperature and developed using the Vistra ECF western blotting kit (Amersham). The results shown in Figure 34 confirm that IGF-I receptor protein is reduced in HaCaT keratinocytes following treatment with oligonucleotides.

EXAMPLE 32

This example shows a reduction in HaCaT keratinocyte cell number following treatment with oligonucleotides. The results are shown in Figure 35. HaCaT cell monolayers were grown at 40% confluence in DMEM containing 10% fetal calf serum treated every 24 hours for 3 days with 2 μg/ml GSV lipid alone (GSV) or complexed with 15 nM oligonucleotide. Cell numbers were then measured every 24 hours using the amido black dye binding assay [32]. Results show that HaCaT keratino cells decrease in number following treatment with oligonucleotides due to a reduction in the anti-apoptotic effect of the IGF-I receptor.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

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